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# OSTEOCHONDRODYSTROPHIA DEFORMANS (MORQUIO BRAILSFORD DISEASE)

BY

N. FELDMAN and M. E. DAVENPORT
From the Coronation Hospital, Johannesburg

(RECEIVED FOR PUBLICATION SEPTEMBER 25, 1950)

In 1929 Morquio described an osseous dystrophy in a family, in which four out of five siblings were affected. In 1931 Brailsford described the radiological features of the disease. Since then about 40 additional cases have been reported in subjects all of European descent. Of the four cases presented in this paper, two are pure Africans and two are of mixed European-African racial origin.

Little is known about the aetiology or pathology of the disease except that many of the cases show a familial and hereditary tendency, but in some instances only a single member of a family has been affected. Shelling (1947) is of the opinion that a dominant Mendelian factor is involved as in achondroplasia, but in the family described by Jacobsen (1939) 20 members belonging to five generations were affected; the hereditary trait appeared to be a sex-linked recessive character. Consanguinity of parents and paternal grandparents was reported by Morquio, but this has not been a feature of all the cases described. In three of our cases a history of consanguineous parents was obtained.

### Case Reports

**Cases 1 and 2.** The subjects reported here are both female siblings (Fig. 1). They are the eldest (7 years) and the youngest (1 year 2 months) of three sisters. The unaffected sibling, aged 3 years, is apparently normal in every respect and shows no radiological changes in the skeleton. Both the affected children were full term normal infants at birth, were breast fed, and sat up, crawled, and walked at the normal age. In both, the mother noticed that from about the age of 1 year they had difficulty in breathing because of ' blocked noses.'

The mother is of pure Bantu stock but the father is coloured (mixed). The parents' mothers were first cousins. Neither can recall any deformity in members of their respective families. Both parents are healthy. Before the birth of the first child the mother had a premature labour at 32 weeks. During her subsequent pregnancies she enjoyed good health and her deliveries were all normal.

CASE 1. T.M., a girl aged 7 years, sat up at 6½ months, crawled at 7 months, and walked before the age of a year. At the age of 3 years the mother noticed that the child was ' knock-kneed and had swelling of her wrists'. She had always had a blocked nose and nasal discharge. At the age of 4 years her tonsils were removed.

Examination revealed a well nourished, intelligent, and cooperative child. The head appeared large, the circumference 21 in. (normal 20½ in.). The hair was dry and wiry, the eyelashes long and curled, the nose broad and flattened at the base. The external nares were filled with thick discharge. The enamel of the

FIG. 1

teeth was poorly calcified especially on the incisors; the dental eruption was normal for the age. The pharynx was congested and there was a thick post-nasal drip. No abnormalities were noted in the heart, lungs, abdomen, or central nervous system.

The standing height was 36 in. (normal 46 in.), the sitting height 20 in. (normal 23 in.), and the weight 32 lb. (normal 50 lb.). The standing position was one of semi-crouching with the knees flexed, and the gait was waddling and on a broad base.

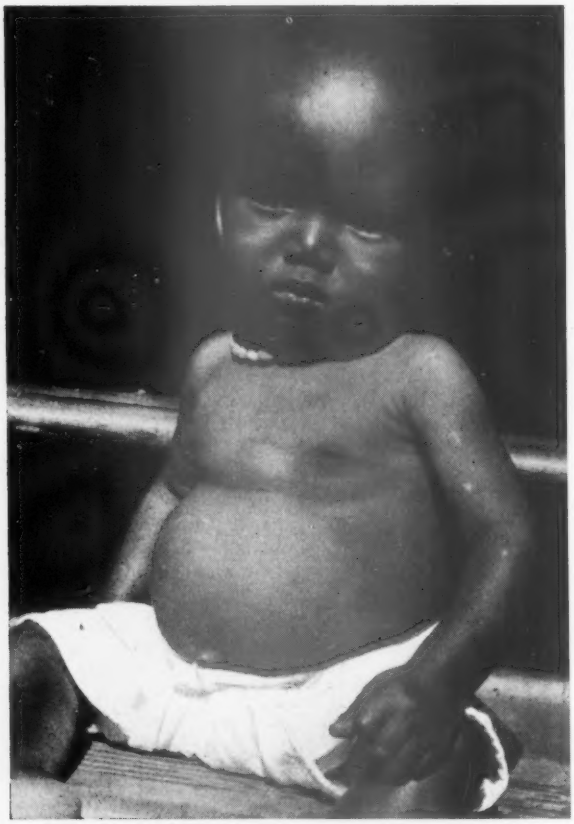


FIG. 2a

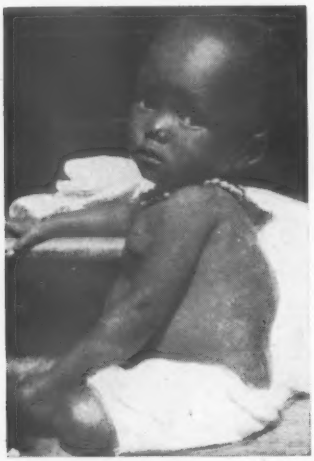


FIG. 2b

The chest was deformed with deep Harrison's grooves. The costochondral junctions were bulbous and the deformity of the pigeon chest was most obvious in the upper sternum. The neck was short and the chin one inch above the sternum. There was splaying of the costal margins.

The abdomen was pot-bellied and there was kyphosis of the lower dorsal region.

The cubitus valgus, ulnar deviation of the wrists, and radial deviation of the phalanges gave the limbs a zig-zag appearance.

Crepitus was present in both shoulder and elbow joints. Extension was limited at the elbow joints and radial deviation at the wrist joints.

The transverse diameter at the ends of the bones was increased, especially at the wrists.

There was an extreme degree of bilateral genu valgum and pes planus. Extension was limited at the knees and eversion at the ankles. There was varus deformity and crepitus at both ankles. The patellae were present and normal. The epiphyseal enlargements were not as pronounced as in the upper extremities. Muscular power was good in all limbs.

CASE 2. J.M., a girl aged 14 months, sat up at 6 months, walked at 1 year, cut the first tooth at 6½ months. She was unable to talk. For the past three months her nose had been blocked and her respiration had been noisy. At 10 months her mother noticed that her back was becoming hunched.

Examination revealed a well nourished child (Figs. 2a and b). The skull appeared large; circumference 18¾ in. (normal 18¼ in.). The anterior fontanelle had a diameter of 2 cm. The nose was flat and the bridge depressed. The external nares were filled with thick mucopus. The pharynx was congested and the tonsils enlarged. The neck was short.

The chest wall bulged anteriorly, the costochondral junctions were thickened and there were well marked Harrison's grooves. The heart was not clinically enlarged and the heart sounds were normal. The air entry to the lungs was poor. There was an impairment of the percussion note at the right base and the breath sounds were diminished on the right side. The abdomen was protuberant with an umbilical hernia. The liver was enlarged 2 in. below the costal margin.

The wrist epiphyses were thickened and there was slight anterior bowing of the tibiae. There was only slight genu valgum, and valgus deformity at the ankles. There was kyphosis, most marked in the lumbar region, and a lateral scoliosis.

The deformities at the other joints were similar to those described in case 1, but of a very much lesser degree.

**Case 3.** The patient was the youngest of a family of six children aged 20, 15, 11, 7, and 1 year and 8 months respectively. He was the second born of a twin delivery. The siblings were all healthy and were not deformed. Both parents were healthy and of pure Bantu stock. Neither could recall any deformity among members of their respective families. The parents were first cousins.

N.M., a boy, aged 20 months, was admitted to the

ward in May, 1948, with a provisional diagnosis of tuberculosis of the spine. Since birth his growth and development had been slower than his twin brother's. The mother noticed that at the age of 3 months his back was not straight. From the age of 5 months the twins attended the local child welfare clinic. The records there show that at the first attendance N.M. weighed 7 lb. 15 oz. and his brother weighed 8 lb. 10 oz. A year later the patient weighed 12 lb. and his brother 16 lb. The patient started to crawl at the age of 7 months, had two teeth at one year, and on admission could only stand supported, and when assisted walked very unsteadily on a broad base. His twin brother walked well at 14 months.

The patient appeared moderately well nourished but was small for his age. The skull showed bossing of the frontal and parietal regions. The circumference was 18½ in. (normal 18½ in.). The anterior fontanelle was open and the diameter was 1½ in. The posterior fontanelle was closed. The root of the nose appeared depressed and the inter-orbital diameter was ⅞ in.

The thoracic cage showed bilateral well-formed Harrison's grooves, with a pigeon breast deformity, the most prominent anterior projection being at the level of the nipples.

The abdomen was ' pot bellied ' with a circumference of 19½ in. ; the liver was enlarged and firm, the edge being palpable 1½ in. below the costal margin. There was prominent kyphosis in the lower dorsal area. The upper extremities showed no deformity and the lower extremities were thin but not deformed.

**Case 4.** E.T. was a boy aged 10 years (Fig. 3). His father died when the patient was 3 years old. His three siblings by his mother's second husband were normal. There was no evidence of deformities in the patient's parents or in their families. The mother was of pure Basuto and the father of pure Xosa stock. The parents were not consanguineous.

The mother stated that pregnancy and delivery were normal and that it was only at the age of 14 days that she noticed that he had a deformity of the back. He was admitted for this complaint to a hospital where he remained for three months, without improvement. His development, both physical and mental, was very slow. He started to walk at the age of 2 years, and speech started only when he was 5 years old. He was mentally retarded and was in a junior grade class at school.

The patient was well nourished, and his stature was small for his age (standing height 44 in.). The skull appeared large, the circumference 22 in. (normal 21 in.), and the nose flat. The intra-orbital diameter was 1⅛ in. The teeth were normally developed. There was no gross deformity of the chest, the circumference of which was 23 in. The costochondral junctions were more prominent than normal. No abnormality was detected in the heart, lungs, or abdomen.

There was marked kyphosis in the upper dorsal region with a large dimple ½ in. by ¼ in. over the spine of the ninth thoracic vertebra. The neck appeared short as a result of the kyphosis. The extremities appeared normal except for the hands which were small and the fingers short and stubby. There was slight ulnar deviation at the wrists and slight inversion of the feet. There was no limitation of movement or crepitus at any of the joints.

### Blood Chemistry

Two of the cases described by Morquio had blood calcium levels of 5·2 mg. and 4·5 mg. respectively. As a result of these findings he stated:

> ' Radiography visualizes the characteristics of the osseous changes, presenting a profound alteration in osteogenesis explicable by the great diminution of the blood calcium.' (Morquio, 1929)

FIG. 3

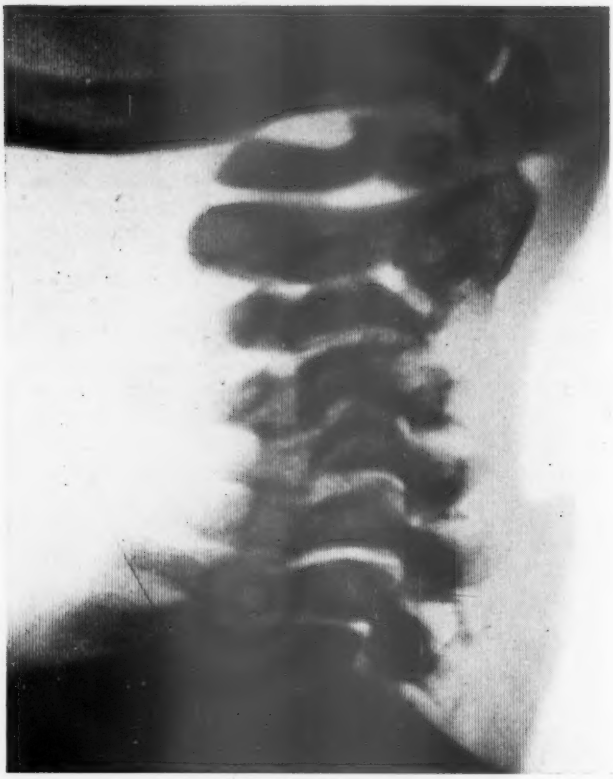


FIG. 4

FIG. 5a

FIG. 4.—Radiograph showing loss of normal cervical lordosis and irregularity of cervical bodies in Case 4.

FIG. 5a.—Radiograph showing the dorso-lumbar kyphosis with anterior tongue-like projections of the lumbar vertebrae in Case 1. The bodies are irregular in size.

FIG. 5b.—Radiograph showing the dorso-lumbar kyphosis and anteriorly tapering bodies in Case 2.

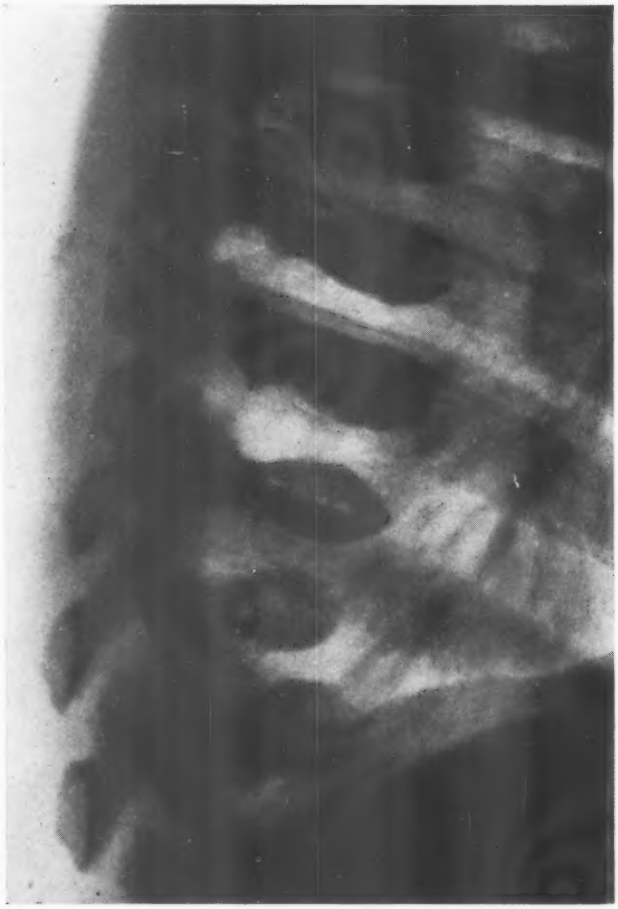


FIG. 5b

FIG. 5c.

FIG. 5c.—Radiograph showing the dorso-lumbar kyphosis and wedging of the body of D12 in Case 3.

FIG. 5d.

FIG. 5d.—Radiograph showing increase in the dorsal curve and irregularly tapering anterior portions of the bodies in Case 4. The bodies are irregular in density.

FIG. 6

FIG. 6.—Radiograph showing that the vertebral bodies are wide and flattened and their structure indefinite (Case 4). The disc spaces are widened.

FIG. 7a and b.—Radiograph shows the irregularly expanded diaphyses of the radius and ulna with overgrowth in length of the radius (Cases 1 and 2).

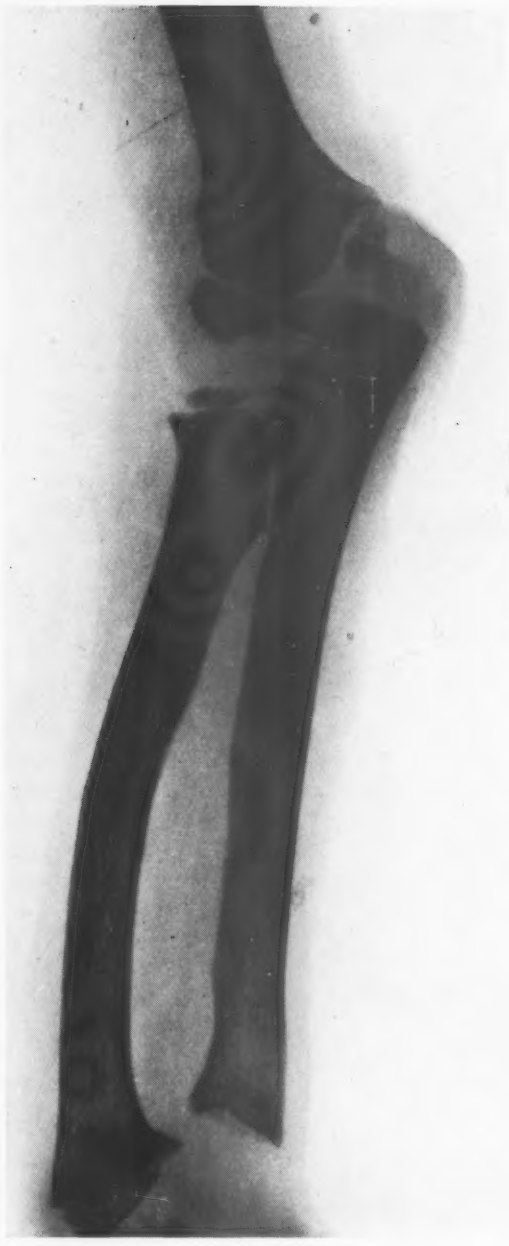


FIG. 7a

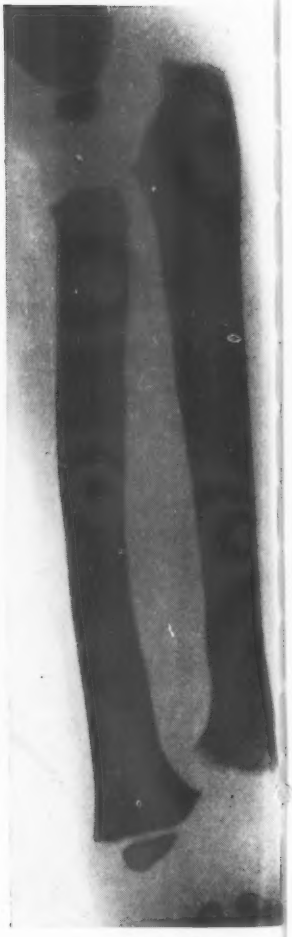
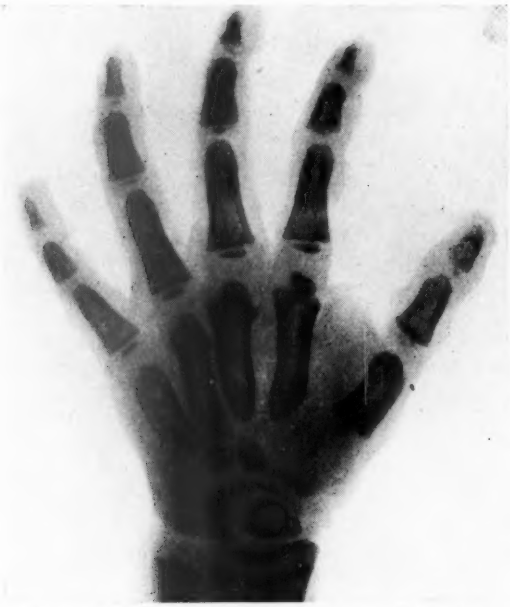


FIG. 7b



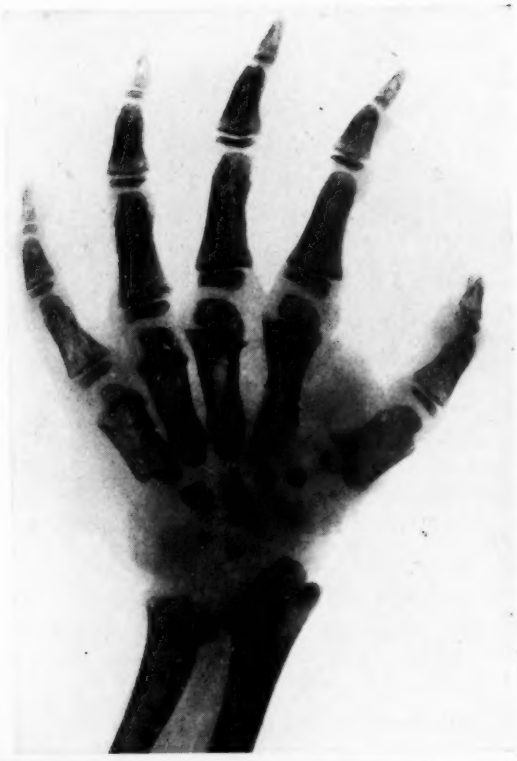


FIG. 8a and b.—Radiographs showing that the metacarpals are stunted with irregular diaphyses (Cases 1 and 2). The trabeculation is irregular. The phalanges are short and thick.

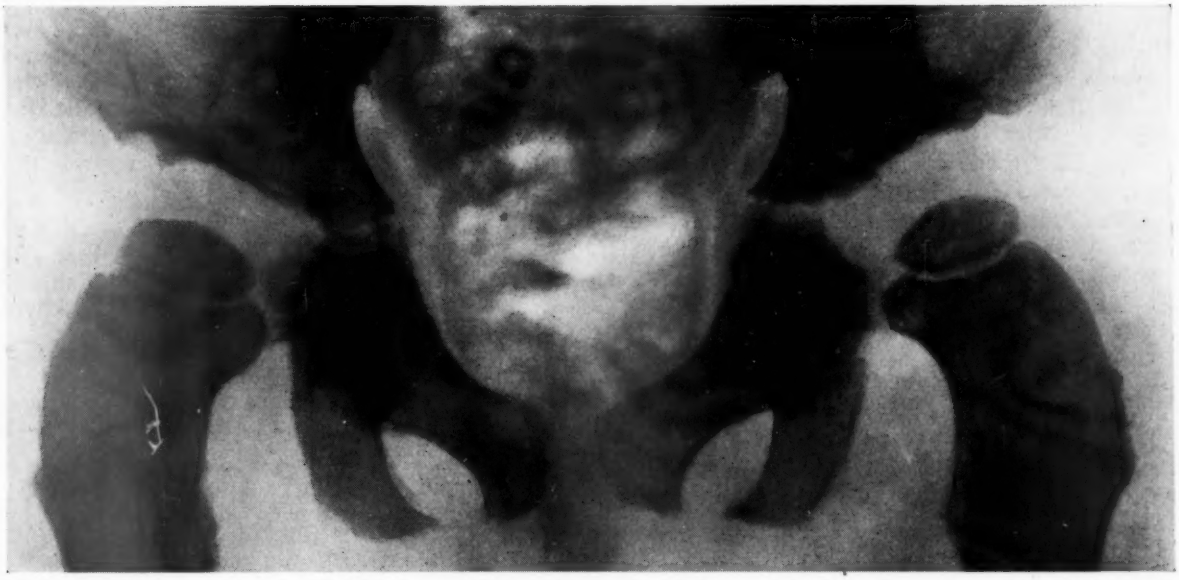


FIG. 9.—Radiograph showing that the acetabuli are wide and irregular and the hip joint spaces widened (Case 1).

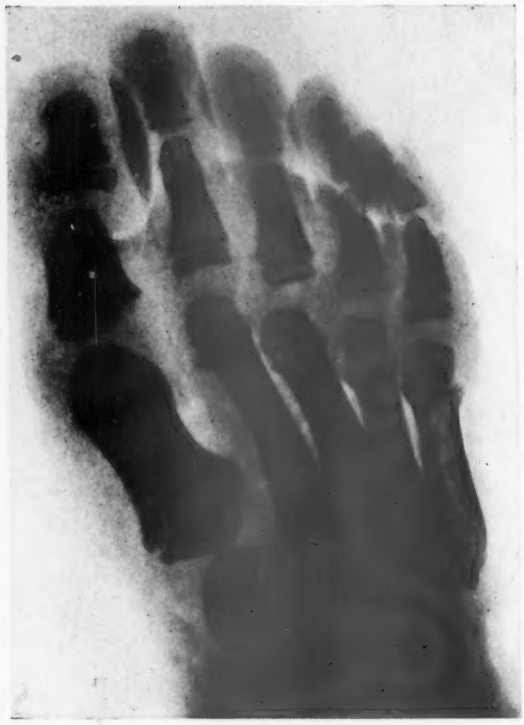


FIG. 11.

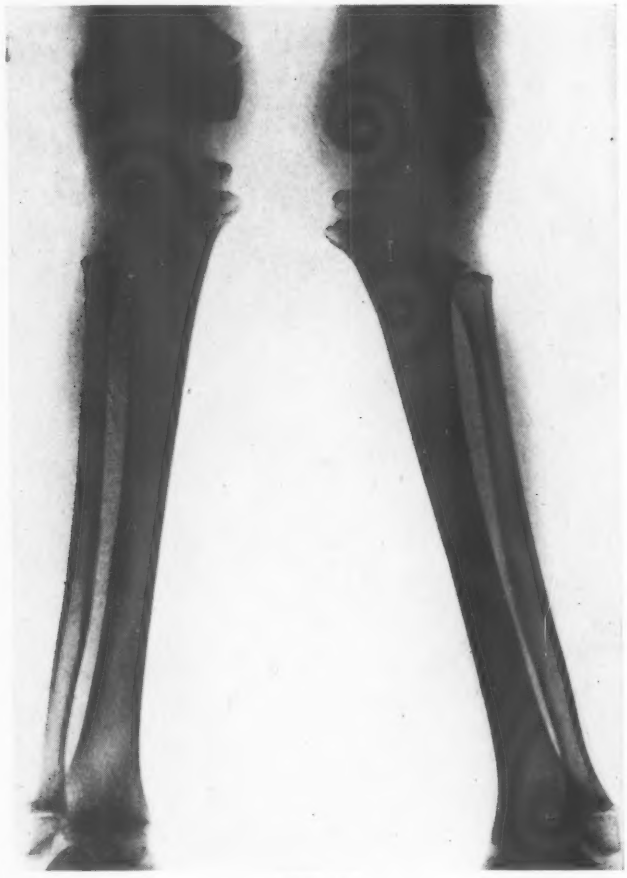


FIG. 10.

FIG. 10.—Genu valgum deformity is shown with irregular proximal tibial diaphyses which slope laterally (Case 1).

FIG. 11.—The metatarsals are thick and short, the proximal diaphyses irregular, and the trabeculation coarse (Case 1).

Hypocalcaemia does not appear to be present in the majority of the other cases described. Shelling (1947) found values varying from 8·7 mg. to 12·8 mg. Meyer and Brennemann (1932) reported a case in which the blood calcium value was 12·8 mg. at the age of 5 years and 10·8 mg. at the age of 6½ years. In eight cases described by Ruggles (1931) the blood calcium was normal. Similarly normal values have been found in respect of blood sugar, phosphorus, cholesterol, and alkaline phosphatase estimations in the reported cases. The blood chemical investigations in our cases are shown in Table 1.

The abnormal values for the serum proteins and the slight anaemia are both probably due to the poor nutrition (low protein diets) of most African native children.

### Radiological Findings

**Alterations in Curvature.** The four cases described all showed alterations in curvature. In case 1 there was loss of the normal cervical lordosis. Cases 1, 2, and 3 showed a kyphosis at the level of D11 and 12. Case 4 showed no dorso-lumbar kyphosis, but the normal dorsal curve was increased.

In case 1 the vertebral bodies of C3, 4, 5, 6, and 7 were irregular in density and their anterior portions ragged and frayed. The dorsal vertebrae in all the cases were irregular in outline, tapering anteriorly, some showing anterior tongue-like projections. The disc spaces were widened, and the epiphyseal plates in case 4 were irregular. Cases 1, 2, and 3 showed the lumbar spinous processes to be short and stunted.

In the antero-posterior projection the vertebral bodies appeared wide and flattened and their structure indefinite.

**Skull.** In two of the cases the calvarium appeared large, and in case 1 there was basilar impression and the root of the nose was depressed. In case 2 the skull showed no obvious abnormality.

**Chest and Ribs.** The antero-posterior diameter of the chest was increased, and the anterior ends of the ribs expanded and somewhat irregular.

TABLE 1

BLOOD CHEMISTRY INVESTIGATIONS

| Investigation | Case 1 | Case 2 | Case 3 | Case 4 |
|---|---|---|---|---|
| Serum calcium | 11·4 mg. % | 11·7 mg. % | 9·4 mg. % | 10·8 mg. % |
| Inorganic phosphorus | 4·0 mg. % | 3·2 mg. % | 4·2 mg. % | 3·4 mg. % |
| Alkaline phosphatase (King-Armstrong units) | 10·7 | 15·5 | 13·8 | 18 |
| Serum albumin | 3·7 g. % | — | 3·9 g. % | — |
| Serum globulin | 2·3 g. % | — | 4·2 g. % | — |
| Blood cholesterol | — | — | 100 mg. % | — |
| Wassermann test | Negative | Negative | Negative | Negative |
| Blood count | Normal | Slight anaemia | Slight anaemia | — |
| Urine | No abnormalities | No abnormalities | No abnormalities | — |

**Shoulder Girdle.** Cases 1 and 2 showed irregularity of the glenoid cavity, and in case 1 the coracoid process appeared expanded.

**Humerus.** The shaft appeared thicker than normal and the proximal epiphyses irregular and uneven in density. The proximal end of the diaphyses was widened and the distal epiphyses fragmented and irregular.

**Radius and Ulna.** These appeared thicker than normal. The proximal and distal diaphyses were irregular and expanded and the articular surfaces sloped towards one another. Cases 1 and 2 showed overgrowth in length of the radius.

**Metacarpals.** These appeared stunted, with irregularity of the proximal and distal diaphyses, the proximal appearing tapered. The shafts showed irregular trabeculation.

**Phalanges.** These were short and thick and the distal phalanges were conical in shape.

**Pelvis.** The acetabuli were widened and irregular and the hip joint spaces widened.

**Femora.** The shafts appeared shorter and thicker than normal and the necks widened. These cases showed bilateral genu valgum, and in addition case 1 showed a marked coxa valga deformity, and the capital epiphyses were irregular in density. The distal end of the shaft was expanded and the knee joint spaces widened.

**Tibia and Fibula.** These appeared thick and short and the proximal end of the tibia expanded, irregular, and sloping laterally.

**Metatarsals.** Basically these bones showed the same features as the metacarpal bones. They appeared thick and short and the proximal ends irregular. There was splaying out of the distal ends of the shafts of all the metatarsal bones except the first. The trabeculation appeared coarse.

## Discussion

Osteochondrodystrophia deformans is a rare familial disease which has hitherto been described in European subjects only. Two of our cases are African native children who have no evidence of European ancestry. In these children the disease is localized to the vertebral bodies with little involvement of the rest of the skeleton. Our other two cases are sisters whose father is of mixed European and African racial origin. They suffer from the generalized form of the disease with involvement of the whole skeleton. The blood chemical findings in our cases do not support the contention of Morquio that hypocalcaemia plays a dominant role in the production of the osseous changes. Although mental retardation is not a feature of the disease, one patient was mentally retarded. In addition, he had a dimple in the skin in the midline over the ninth thoracic vertebra. In a case of gargoylism described by Ellis (1940) mental retardation, which is a feature of that disease, was not present. This patient also had a midline skin dimple in the region of the first lumbar vertebrae.

The purulent rhinitis which was such a troublesome feature in two of our cases has been described as a feature of gargoylism, where it is caused by the nasal malformation (Henderson, 1940). It is understandable, in view of these common signs and symptoms, why cases of Morquio Brailsford disease have been wrongly labelled gargoylism and vice versa.

Morquio Brailsford disease is probably due to a hereditary developmental defect in germ plasm and is a dyschondroplasia. The hereditary disturbances of regular cartilage growth manifest many different syndromes. They may be classified in four main groups, but it should be remembered that considerable overlapping may take place. The blood

calcium, phosphorus and alkaline phosphatase blood levels are normal in all.

**Group I. Hypoplasia of Cartilage.** Achondroplasia results from the failure of normal cartilage development. It causes dwarfism and osseous changes in which the tubular bones become reduced in length and are trumpet-shaped. The epiphyses are normal. The vertebrae may occasionally show wedge-shaped deformities.

**Group II. Irregular Cartilage Growth and Distribution.** Multiple chondromata is a familial disorder characterized by the presence of bilateral symmetrical chondromata usually involving the phalanges and small bones of the hands and feet.

Ollier's disease is a dyschondroplasia which is recognized by the presence of non-ossified cartilage in the diaphyseal ends of bones. The distribution of the lesions is usually unilateral and facial asymmetry is present in many cases.

In diaphyseal aclasis, a familial disorder, there are exostoses covered by hyaline cartilage in the diaphyses of the long bones near the epiphyseal plates.

**Group III. Hyperplasia of Cartilage Growth.** This group contains osteochondrodystrophia deformans (Morquio Brailsford disease).

**Group IV. Combinations of Chondrodysplasia with Ecto- and Meso-dermal Defects.** (1) Gargoylism (Hurler's disease) has been confused with the generalized type of Morquio Brailsford disease. In addition to the cartilage irregularities there are hepatosplenomegaly, mental changes, corneal opacities, and profuse purulent rhinorrhoea.

(2) Chondro-ectodermal dysplasia was described by Ellis and van Creveld (1940) in three infants with bone changes resembling achondroplasia but without involvement of the base of the skull. In addition there were polydactyly, defects of the hair and nails, and congenital morbus cordis.

(3) In Maffucci's syndrome the dyschondroplasia is associated with multiple angiomata.

Many other syndromes may occur in which combinations of the various chondral growth disturbances are associated with ecto- and mesodermal abnormalities. We recently saw a young Indian girl who had bone changes resembling achondroplasia in one half of the skeleton and changes of osteochondrodystrophia deformans in the remainder of the skeleton.

**Summary**

Four cases of osteochondrodystrophia deformans (Morquio's disease) are described.

Two of the cases are of pure African native stock but the others are of mixed African and coloured stock. These appear to be the first reported cases occurring in persons not of pure European racial origin.

Consanguinity of the parents is present in three cases.

The blood chemistry investigations show no significant departure from normal.

A close relationship exists between the many different varieties of dyschondroplasia.

The patients were admitted to the paediatric unit of the Coronation Hospital under Dr. S. Selby. We wish to thank him for permission to publish the case reports and for his interest and encouragement.

We are indebted to Dr. M. Findlay for helpful advice on the radiological aspects, and to Dr. E. Samuel for advice and assistance in the preparation of this paper.

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# CONGENITAL MYASTHENIA GRAVIS

BY

R. I. MACKAY

From the Hope Hospital, Salford

(Received for Publication April 10, 1950)

This report of a case of congenital myasthenia gravis and a study of the patient's family are presented not only because of their intrinsic interest, but also because they may help to elucidate this rare condition and to establish it as a disorder of infancy.

The accounts of myasthenia gravis in the textbooks do not usually include references to the condition in infancy. The maximal incidence is in young adults, but many articles have reviewed the cases known to have occurred in childhood. The condition has, however, only rarely been reported in infants.

Levin (1949) described congenital myasthenia gravis in two siblings, and reviewed previous case reports. From these he deduced certain clinical principles concerning the behaviour of myasthenia gravis in young infants.

The case reports can be analysed in three groups.

The first group may be classified as transitory neonatal myasthenia occurring in infants whose mothers suffer from myasthenia gravis. They all show signs of a myasthenic state: general feebleness, poor sucking and swallowing reflexes, drooping eyelids, a mask-like facies, and sometimes sudden, fatal collapse. When such infants were treated for the first two weeks of life with prostigmine, survival and recovery were usual. If prostigmine was not continued, the infants usually died, some after a sudden collapse. Strickroot, Schaeffer, and Bergo (1942) reported such an infant who developed symptoms on the third day, and in whom 3·75 mg. of prostigmine bromide, given orally, produced a dramatic response. Omission of the treatment on the fifth day caused a relapse, and although some recovery followed the administration of a double dose, the baby suddenly collapsed and died. At necropsy there was evidence of cerebral congestion and oedema, atelectasis, suprarenal haemorrhages, and diffuse cloudy swelling of other organs with mild hyperplasia of the thymus including hypertrophy of Hassall's corpuscles. Wilson and Stoner (1944) reported two probable cases born to a woman with myasthenia gravis; the first died soon after birth, while the mother was not receiving treatment; the second survived after some initial difficulties, while the mother was having regular maintenance treatment with prostigmine. Neither infant received prostigmine as treatment. Stone and Rider (1949) reported a similar case in which the infant was treated with neostigmine for 14 days, and who survived as a normal child. LaBranche and Jefferson (1949) described a child who responded to prostigmine therapy which was continued for four months. At this age the child's condition was reported as satisfactory, while treatment continued. F. R. Ford reported to Levin, in a personal communication, a baby born with a myasthenic state, who was treated for one week and survived as a normal infant. The various authors imply that this type of myasthenia is due to the transplacental passage of a curare-like substance which affects the baby at birth, but which is destroyed in some manner, and leaves the child unaffected in later life.

In the second group, three cases of congenital myasthenia gravis have been reported in which the accepted clinical picture of myasthenia gravis was present from birth. The mothers were not affected. Bowman (1948) described a child in whom the condition had been present from birth, and who was well maintained on prostigmine. Two cases were described by Levin in the paper quoted. The first was a boy whose symptoms were present from birth as progressive weakness, bilateral ptosis, and limited ocular movements. He responded well to prostigmine therapy, but treatment was discontinued during an acute respiratory infection, and he died. The second case was the boy's younger sister whose condition was suspected in the antenatal period, because the mother felt that foetal movements were not sufficiently strong. Myasthenia gravis was diagnosed at birth, and treatment started at once. Treatment was continuous, and the response satisfactory. The mother was not affected, and no latent myasthenic state could be demonstrated even after large doses of quinine.

Although no other cases of congenital myasthenia gravis have been reported, Levin states certain principles concerning the condition. He suggests

that in certain circumstances, diminished foetal movements may be noted, implying a prenatal inception of the disorder. He also states that congenital myasthenia gravis differs from the acquired condition in the symmetry of muscular weakness, and that the disorder is neither progressive nor intermittent.

The third group of cases should be called 'infantile' rather than 'congenital,' though the onset of symptoms is noted so early in life that a congenital disorder may be suspected. These cases are often diagnosed after a respiratory infection, and in more than one report there has been a familial incidence. Bowman's cases (1948) include two cousins, and Rothbart (1937) described a family in which four boys were affected, the youngest developing symptoms at the age of six weeks. In this family the course was intermittent and one boy died. A sister was unaffected.

### Case History

The patient is the first born of twin girls born on February 5, 1942. The mother was 30 years old at the time of the confinement, and it was her first pregnancy. The antenatal period was uncomplicated until the 36th week when there was mild hypertension. At term there was heavy albuminuria, and a diastolic blood pressure of 100 mm. Hg. After treatment, she was successfully delivered of twins by natural forces. There was only one placenta, which was expelled intact with membranes.

The patient presented by the vertex, and weighed 5 lb. 3 oz.; her twin, a breech delivery, weighed 3 lb. 12 oz. At the age of 18 days, the twin had gained 1 lb. 1 oz. in weight; the patient who had not regained her birth weight, equalled her sister at 4 lb. 13 oz. The patient was discharged from hospital at the age of 20 days weighing 5 lb. 1 oz. The twin was discharged at 32 days, weighing 5 lb. Both babies were initially fed on breast milk, the twin requiring a complementary feed of milk formula. Artificial feeding was necessary soon after she left the hospital.

The mother, who is a reliable witness, described the patient as 'a silly feeder though hungry,' and 'a weakly baby from birth,' whereas her twin was 'a normal baby.' She was overtaken by her twin in growth and progress at 3 months of age. Because of the feeding difficulties, the mother attended a hospital out-patient department when the patient was 3 months old. She was told to enlarge the hole in the teat of the feeding bottle, and given other instructions in feeding technique which she faithfully carried out. The baby did not improve, and seemed too feeble to suck properly. Her twin often finished both feeds.

The children (Fig. 1) attended the welfare centre when they were 1 year old, the mother complaining that the patient was late in walking, and did not jump and play like her sister. At the age of 3 years, she attended hospital on account of bilateral ptosis, and weakness of the legs, but no diagnosis was made. The ptosis was later complicated by photophobia. At the age of 4 years she could walk but could not run nor jump (Table 1).

FIG. 1.

TABLE 1
COMPARISON OF PATIENT'S AND TWIN'S MILESTONES

| Activity | Patient | Twin |
|---|---|---|
| Sat up.. .. | at 5–6 months | 5–6 months |
| Walked .. | at 15–16 months | 10–12 months |
| Running .. | Only recently | Since infancy |
| Talked .. | at 1 year (first) | 1 year (second) |
| First tooth .. | 6 months | 9 months |

A comparison of the performance of the two children shows that the patient eats more slowly, though she may eat more than her twin. There is the greatest difficulty at tea time, though there has never been any nasal regurgitation. The patient finds swallowing and nose blowing difficult. She is easily roused in the morning, but tires more quickly than her sister. She never hurries; she falls clumsily, and then has difficulty in getting up again. She sweats more than her sister.

The ptosis was first noticed as abnormal in her third year, and it has increased progressively, though less in the early morning; it becomes maximal within half an hour of rising. Movements of the eyes have steadily decreased until they are now almost stationary. She has always been poor at 'face-pulling.' There have been no variations in the degree of weakness, no remissions and no crises of respiratory failure.

In her intellectual activity she is superior to her twin; she is the leader, and speaks more fluently.

No other member of the family is known to be affected.

At the first attendance she was 7 years 8 months old and on examination she was 42¾ in. tall and 37 lb. 1 oz. in weight, while her sister was 45 in. tall and 47 lb. 13 oz.

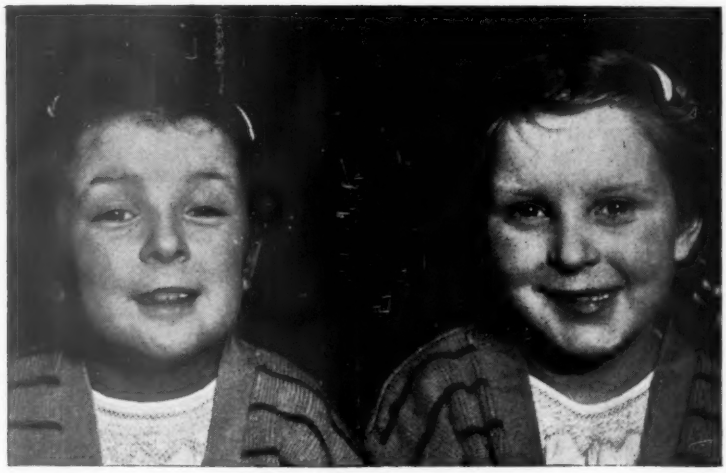

FIG. 2.

in weight. She appeared to be less well nourished than her twin (Fig. 2).

Her face was expressionless, and typically myopathic with bilateral ptosis to the pupil rim, and this caused her to throw her head back in order to see across the room. She had a complete external ophthalmoplegia. Voluntary movements, such as wrinkling the forehead, wrinkling the nose, and opening the eyes widely were virtually impossible. Persistence of grip was poor, that is to say the power to grip was poor in itself, though fatiguability was difficult to judge, because she could not maintain a constant grip. Repetitive movements were not well done, and the impression was gained that her performance was definitely inferior to her sister's. Full clinical examination did not reveal any wasting of skeletal muscles, and no abnormality was found in other systems.

Further laboratory investigation furnished the following information; the norms are taken from Behrendt (1949), quoting Harding and Gaebler.

| | Patient | Twin |
|---|---|---|
| Radiograph of chest .. | No abnormality | — |
| Radiograph of skull .. | No abnormality | — |
| Wassermann and Kahn reactions .. .. .. | Negative | — |
| Urinary creatinine coefficient (Norm for age—less than 18·1) | 19·8 | 16·3 |
| Urine creatine coefficient .. (Norm for age—less than 4·5) | 6·1 | 1·25 |

In view of an earlier suggestion that the twins were uniovular, and because of the implications of such a relationship, it was felt necessary to obtain further evidence on this point.

Fig. 2 indicates that the children are not identical in appearance; nor are they identical in measurements or in their personalities. It is not clear to what extent this is the result of the limitations imposed on the patient by her condition. The patient's hair is darker than her sister's, though both could be classed as blonde. The twin has a clear blue iris, while the patient's iris is a darker blue, and is slightly more pigmented.

Expert opinion was sought on their fingerprints which proved to be dissimilar. The degree to which they differ suggests that the children are binovular twins. The formulae, according to the Edward Henry classification, are as follows:

$$\text{Patient } \frac{\text{O. A. AII. 6}}{\text{O.aA. AMM. 12}}$$

$$\text{Twin } \frac{\text{O. U. IMO. 8}}{\text{O. U. MMI. 2}}$$

Detailed study of the blood groups of the whole family was performed, with the following result (Table 2), and this evidence also suggests that the twins are binovular.

TABLE 2
BLOOD GROUP OF PATIENT'S FAMILY

| Group | Father | Mother | Patient | Twin |
|---|---|---|---|---|
| ABO .. | $A_1$ | O | $A_1$ | $A_1$ |
| Rh .. | $R_2R_2$ | $R_1r$ | $R_1R_2$ | $R_1R_2$ |
| MNS .. | MNS | MNS | MS | MNS |
| P .. | Neg. | Pos. | Pos. | Pos. |
| Lewis .. | a−b+ | a−b− | a+b− | a−b+ |
| Kell .. | Pos. | Neg. | Neg. | Neg. |
| Lutheran | Neg. | Neg. | Neg. | Neg. |
| Duffy .. | Neg. | Neg. | Neg. | Neg. |
| Secretor | Secretor (A & H) | Non-secretor (H) | Non-secretor (A & H) | Secretor (A & H) |

An attempt was made to obtain the myasthenic reaction of Jolly, and to assess muscle fatiguability objectively by electrical stimulation, but the child was frightened by the sensations and could not cooperate. The attempt was abandoned.

The therapeutic test was positive. Within 15 minutes of the subcutaneous injection of 1 mg. of neostigmine methyl sulphate with 1/150 gr. atropine sulphate, the ptosis could be overcome completely to show a rim of sclera above the iris (Figs. 3 and 4), facial grimacing was possible, and repetitive actions more sustained, though precise observation was difficult.

Far more obvious and satisfactory were the comments

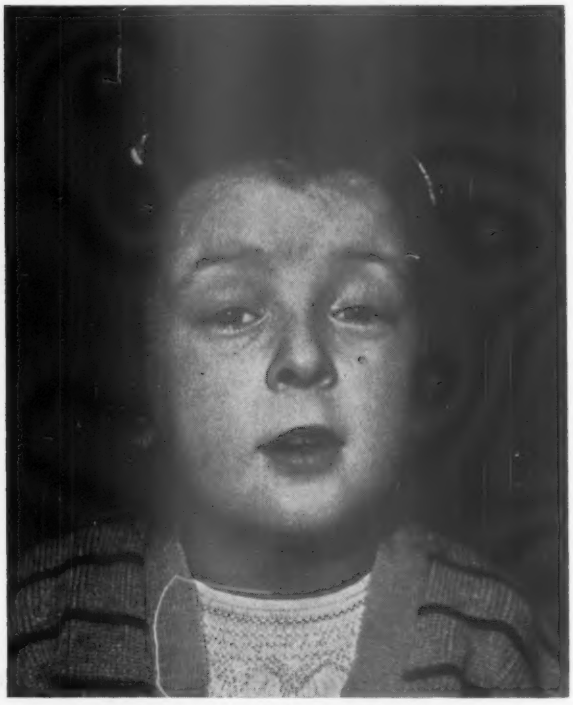

FIG. 3.—Before therapeutic test.

of her mother and friends when she returned home on a maintenance treatment of 10 mg. of neostigmine methyl sulphate by mouth three times daily. ' Her voice is so loud now,' ' she sings and shouts such a lot,' ' I've never seen her run before, and now she runs everywhere,' were her mother's comments. Her school teachers were amazed at her new vigour and energy. Her Brownie leader reported that she took part in games which had previously been beyond her powers. The patient herself is aware of the effect of the powders, and can now feel when one is required. Her mother regulates the daily dosage according to need. In general, she requires 12 mg. three times daily at present, the last dose usually being taken no later than 3 p.m. Apart from her increased activity, she gained 3 lb. in weight and $1\frac{1}{4}$ in. in height in the first six weeks of treatment. Approximately 10 months later her weight was 39 lb. 4 oz. (total gain 2 lb. 3 oz.) and her height $44\frac{1}{2}$ in., showing a total gain of $1\frac{3}{4}$ in., while her sister weighed 47 lb. 14 oz., a total gain of 1 oz., and measured $47\frac{1}{2}$ in., a total gain of 2 in.

Although there was no obvious variation in her myasthenic state before treatment began, she has ' been poorly in the night ' on two occasions in recent months. The attacks have begun with a light dry cough in the early evening which would not respond to homely measures of treatment. During the night, she has been unable to sleep because the cough was persistent, and she became frightened by a feeling of suffocation. She became more exhausted, and eventually slept in the early hours of the morning. The next day she seemed normally active, though sleepy. On these occasions she has had no prostigmine from 3 p.m. in the afternoon until 8 a.m. the next morning and the attacks followed days of unusual excitement or activity.

Bearing in mind the case reports of congenital myasthenia gravis in which there was a familial incidence, it was decided to test the unaffected members of the patient's immediate family for latent myasthenia, using a modification of the curare test as suggested by Bennet and Cash (1943). It was anticipated that the twin might have a latent myasthenic state demonstrable as undue sensitivity to curare.

In consultation with Dr. M. Boyle, it was decided to inject a test dose of d-tubocurarine chloride amounting to approximately 0·2 mg. per stone (0·03 mg. per kg.) of body weight. In fact, both parents received two doses of 1 mg. tubocurarine within four minutes, and the twin received two doses of 0·5 mg. This represents slightly more than 0·2 mg. per stone, but was a more convenient dose to administer. Both before and three minutes after the first injection of tubocurarine, muscular function was assessed by observation of ptosis, ocular movement, diplopia, swallowing, speech, and maintenance of power of repeated grips of the examiner's hand. An ergograph could not be obtained for the test. Three minutes after the second injection the tests were repeated.

At no time did either of the parents or the twin show any alteration in muscle power as demonstrated by these tests; in fact, they did not even show the degree of alteration as shown by ' normal ' patients regarded as ' hypersensitive ' to test doses of tubocurarine. Therefore no myasthenic state could be demonstrated in these members of the patient's family.

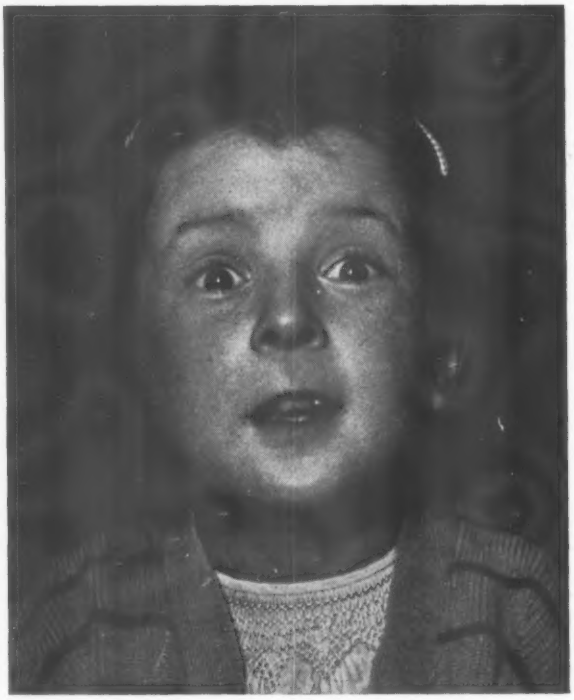

FIG. 4.—Fifteen minutes after therapeutic test.

This child's history agrees in some respects with the observations of Levin. The muscular weakness is symmetrical, and there has been no obvious variation in the severity of the myasthenia. The disability has, however, been slowly progressive from birth, and the nocturnal attacks since the beginning of treatment may be 'withdrawal' symptoms in the late evening rather than true crises.

Although the results of estimations of urinary creatine and creatinine are not completely satisfactory, they do confirm the diagnosis in the patient and are nearer normal in the twin. This is in keeping with the results of the curare test. There is thus no suggestion of a familial incidence. (Wilson and Stoner also mention an adult patient who had a normal twin.)

When considering the aetiology of this disorder in the light of current theories, some difficulties arise. If myasthenia gravis is a constitutional disorder, in what ways do the constitutions of these twins differ?

Wilson and Stoner, discussing the theories of causation, discount the view that cholinesterase metabolism is abnormal on the basis of serum cholinesterase studies. They also show that myasthenic patients produce normal quantities of acetylcholine (it has been noted that the patient sweats more than her twin, but this has not been proved objectively), and do not favour this theory. Their opinion is that myasthenia gravis is due to the action of some 'curare-like' substance blocking the myoneural receptor mechanism. This view is supported by the clinical picture of the condition 'transitory neonatal myasthenia.' A 'curare-like' substance did not produce any observable effect in the normal twin, though it was considered too dangerous to complete the experiment by administering tubocurarine to the patient. Does this imply that some third factor is necessary before symptoms appear in the myasthenic patient? Such a factor would not be excluded by the experiments conducted by Wilson and Stoner, unless it can be excluded in the laboratory frog-muscle preparations used.

**Summary**

A case of congenital myasthenia gravis in one of binovular twins is described.

No latent myasthenic state could be demonstrated in the twin or the parents by injection of d-tubocurarine.

Arising out of this study, certain speculations are made on the aetiology of myasthenia gravis.

I am indebted to a number of persons whose expert knowledge has contributed evidence for this paper. I wish to thank Dr. M. Boyle, consultant anaesthetist to the Salford Hospital Group, who devised and cooperated in the tubocurarine tests; Dr. F. Stratton and Dr. P. Renton, of the National Blood Transfusion Service, for performing the tests of blood groups; Detective Sergeant J. Simpson of the Salford City Police, who examined finger prints; Mr. G. Ward, clinical photographer to the Duchess of York Hospital for Babies, Manchester, for the photographs, and the laboratory and nursing staff of Hope Hospital for their assistance.

My thanks are also due to Professor Wilfred Gaisford for his advice on the preparation of this report, and to the twins and their parents for willing cooperation at all times.

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# FUNCTIONAL INTESTINAL OBSTRUCTION IN THE NEWBORN

BY

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There are very few references in the literature to functional intestinal obstruction in the newborn. Zuelzer and Wilson in 1948 first drew attention to this condition and reported 11 cases, four of which resembled Hirschsprung's disease in older children. Vomiting and gross intestinal obstruction seen after birth were the presenting features in the remaining seven cases, five of which were operated upon and no mechanical obstruction was found; all seven died. Five were submitted to necropsy and the absence of a mechanical cause for their obstructive symptoms was confirmed; in three cases there was evidence of peritonitis. Serial sections of the intestines from three of these infants showed absence of the ganglion cells of Auerbach's plexus of the large intestine extending proximally as far as the sigmoid, caecum, and the ileum respectively. Zuelzer and Wilson were able to correlate the level of obstruction with the level of agenesis of ganglion cells. Five of the seven infants were brothers and sisters in a family of 11 children. A family with similar clinical features is reported in this paper.

### Case History

Michael McG. was admitted to the Royal Liverpool Children's Hospital at the age of 4 days with the following history.

The mother's pregnancy and delivery were normal. The maternal blood was reported to be Rh and Kahn negative at 28 weeks of gestation and no Rh antibodies were present. He was considered to be a normal baby on delivery; the birth weight was 8 lb. 13 oz. and meconium was passed 24 hours after birth. When 48 hours old he vomited, his temperature rose to 104·8°, and his respirations to 90 per minute. The following day he had well established bronchopneumonia and a grossly distended abdomen. On rectal examination the anal sphincter was rather tight and some dry meconium was present in the rectum. A plain x-ray film showed multiple small bowel fluid levels and gross intestinal distension (Fig. 1). He was transferred to the Royal Liverpool Children's Hospital as a case of intestinal obstruction.

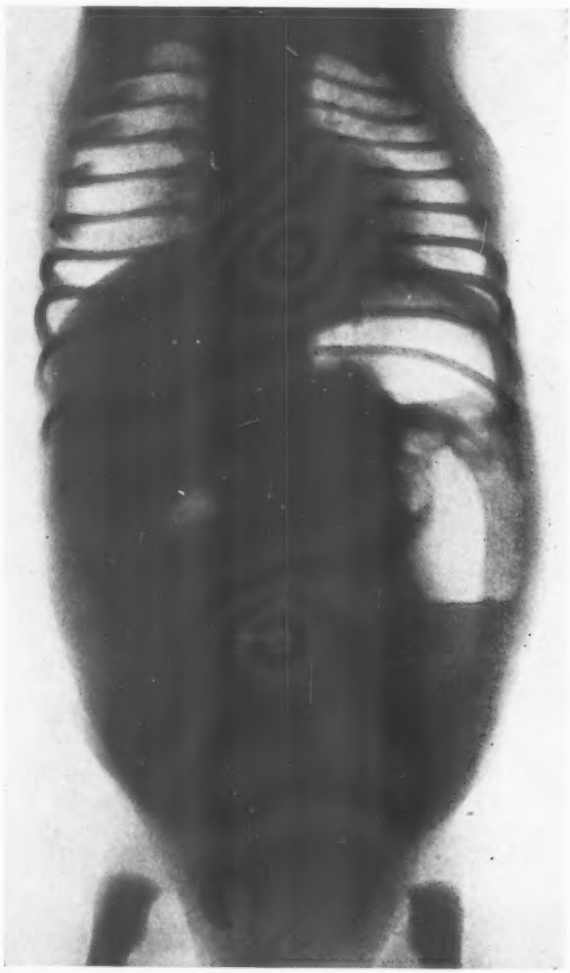

FIG. 1.—Radiograph of Michael McG. showing multiple fluid levels in the small intestine, typical of small gut obstruction.

On admission the general condition was fair; there was very marked distension of the abdomen and two enemata gave no result. Gastric suction and intravenous infusion were instituted. Pancreatic fibrosis as

a possible diagnosis was considered unlikely because trypsin was present in the duodenal juice.

Six hours after admission a laparotomy was performed under endo-tracheal ether, oxygen, and $CO_2$ anaesthesia (Dr. Jackson Rees). The abdomen was opened through a left paramedian incision. The lower jejunum and whole ileum were grossly distended, the caecum and ascending colon moderately so, but the transverse and descending colon were normal in calibre. There was no clear line of demarcation between the distended and normal bowel and no mechanical obstruction. The distended bowel was dusky blue. There was some enlargement of the mesenteric glands but no obstruction to the mesenteric vessels. No other abnormality was noted and the abdomen was closed.

Gastric suction and intravenous fluids were continued post-operatively and the child was nursed in an oxygen tent. Abdominal distension was marked. On the fourth post-operative day he passed a small stool and some flatus, and was given small feeds by mouth. No further stools were passed and the distension recurred in spite of enemata.

On the thirteenth post-operative day he had a violent attack of vomiting and ruptured his abdominal incision. The wound was re-sutured under general anaesthesia and gastric suction and intravenous fluids were reinstituted.

Six days after the second anaesthetic he took feeds well and vomited only occasionally. He was, however, extremely constipated, although enemata produced small stools and some flatus. There were two further episodes of distension and temporary improvement. At 5 weeks of age the vomiting started again, enemata failed to relieve the distension, and the child died.

**Post-mortem Findings.** The body weighed 8 lb. 2 oz. There was marked abdominal distension with wasting of the limbs. Peritonitis was present with numerous abscess cavities, and the coils of intestine were matted together by a thick fibro-purulent exudate. On the anterior aspect of the caecum there was a perforated stercoral ulcer, 1 cm. in diameter. The terminal ileum, caecum, and proximal half of the ascending colon were grossly dilated and thin walled, but the rest of the large bowel was of normal calibre. The whole intestine contained hard, compact, homogeneous, malodorous faeces.

Nothing of significance was found in the remaining viscera including the pancreas.

**Microscopical Findings.** Blocks, both transverse and longitudinal, were taken from the small bowel, vermiform appendix, descending and pelvic colon, and rectum. The most distal blocks came from within a few centimetres of the anal sphincter, but the sphincter ani itself was not included.

From each block four to six sections were cut and stained with haematoxylin and eosin and several frozen sections were stained. Myenteric and sub-mucous ganglia were present in the small bowel and in the ileo-caecal region in normal numbers, but in the caecum the myenteric ganglia became scanty, one or two being found in each section of some 2 cm. in length. Normal ganglia consist of a dozen or more neurons, but these ganglia

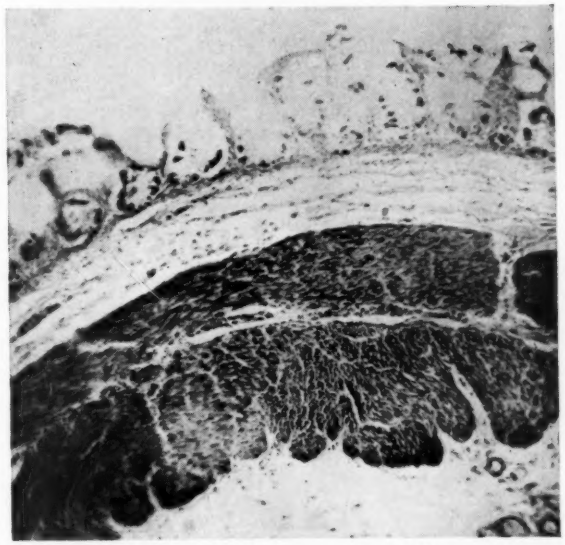

FIG. 2.—Normal colon. Myenteric ganglia can be seen separating the muscle coats. × 56.

showed only two to four neurons. The sparseness of ganglia could in part be explained by the dilatation found at this site and consequent dilution by stretching. The appendix was so inflamed that the presence or absence of ganglia could not be determined.

As the caecum merged into the ascending colon ganglia became progressively more difficult to find, and at about the middle third of the ascending colon, examination of several sections failed to reveal any ganglia. From this point onwards to the last rectal section not a single myenteric ganglion was found. It was thought that the submucous ganglia were absent from the same regions,

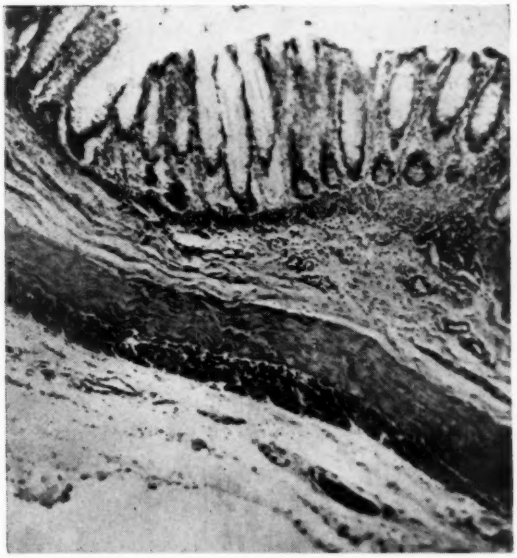

FIG. 3.—Colon of Michael McG. showing closely approximated muscle coats. No ganglia. × 56.

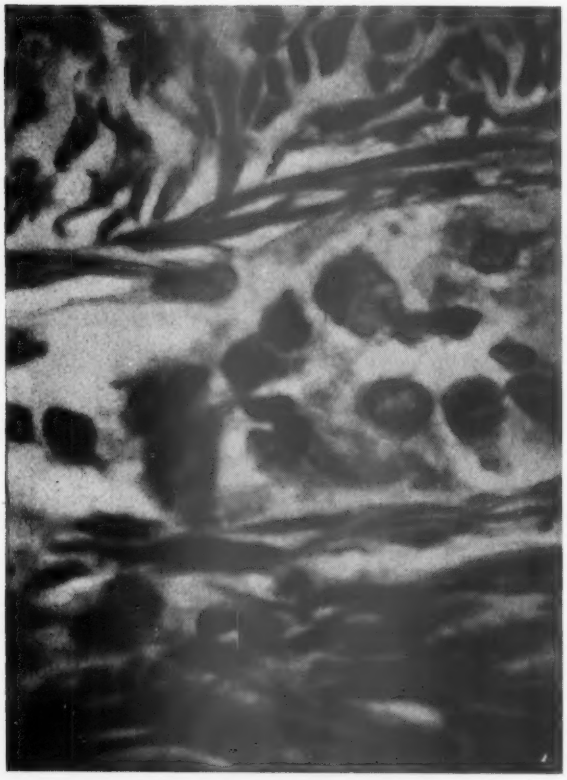

FIG. 4.—Normal myenteric ganglion. × 800.

but the masking effect of considerable numbers of inflammatory cells throughout the submucosa of the greater part of the large bowel made it difficult to establish this impression.

At the hepatic flexure small, non-myelinated nerve bundles, well circumscribed by a delicate connective tissue sheath, were seen coursing between the longitudinal and circular muscle coats. The general direction of these bundles appeared to be longitudinal as they were cut more often at right angles in transverse than in longitudinal sections (Fig. 5). They remained scanty in the proximal colon; distally they increased in size and number becoming both numerous and conspicuous in the pelvic colon and rectum. In the caecum, ascending and transverse colon, the longitudinal and circular muscle coats were closely approximated owing to the absence of myenteric ganglia (Fig. 3). In the descending colon and rectum the normal separation was maintained by the non-myelinated nerve bundles.

The accompanying photomicrographs illustrate the conditions found in the pathological gut. Photographs of normal sections are included for comparison (Figs. 2 and 4).

**Family History.** Michael McG's family tree (see page 300) shows that three of his four brothers and sisters died shortly after birth; two were operated upon at the Royal Liverpool Children's Hospital. One of Michael's maternal aunts has for five years been under treatment for her abdominal condition at the same hospital. The brief case histories of these children are as follows:

(1) Stephen McG. was born on March 30, 1942. The pregnancy and delivery were normal. The birth weight was 7 lb. 11 oz. He died 48 hours after birth. The report of the post-mortem examination, performed at another hospital, reads: 'Congestion of lungs and intestines.' No sections of the intestines were examined microscopically.

(2) Patricia McG. was born on May 19, 1947, following a normal pregnancy and delivery. She was admitted to the Royal Liverpool Children's Hospital at the age of 8 weeks with a history of constipation since birth. At 4 weeks of age vomiting began, and this was temporarily relieved when bottle feeds were given instead of breast feeds, but two days before admission vomiting had started again. On examination the abdomen was seen to be grossly distended and the rectum was full of faeces. An enema yielded a small constipated result. The following day distension was more marked and gastric suction and intravenous infusion were started. At laparotomy there was dilatation of small and large intestine with some pus in the right iliac fossa. The appendix was not found. The abdomen was closed with drainage. Post-operatively the belly remained distended and gastric suction and intravenous infusion were continued. She improved and took feeds quite

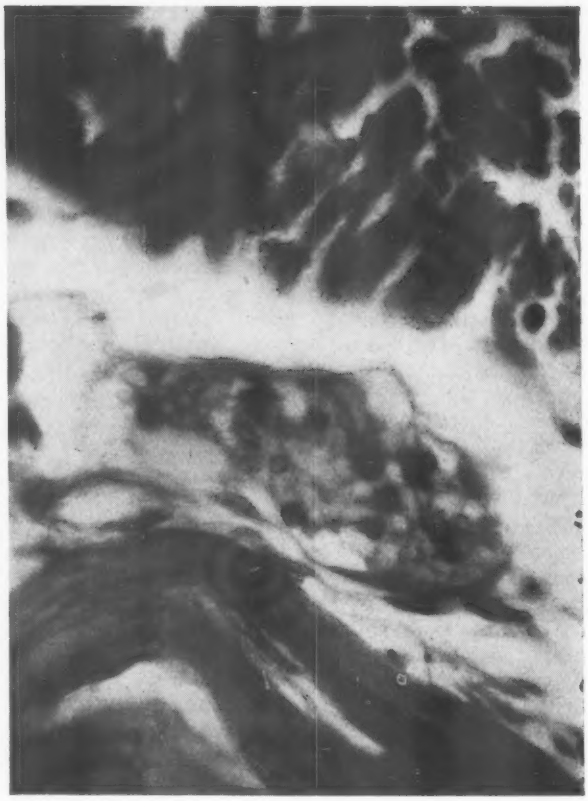

FIG. 5.—Plexus from Michael McG. Ganglionic neurons absent. × 800.

well but remained very constipated. Four weeks later her condition deteriorated, there was gross distension, and she died at the age of 14 weeks. Post-mortem examination revealed multiple adhesions and pockets of pus in the abdomen. There was no mechanical obstruction. No sections were taken from the intestine for microscopical examination.

(3) Anthony McG. was born on October 10, 1948, after a normal pregnancy and delivery. His birth weight was 7 lb. 11 oz. He was admitted to the Royal Liverpool Children's Hospital when one day old with a history of vomiting bile. The abdomen was distended and an enema yielded a small amount of meconium. Intravenous saline and gastric suction were started. At laparotomy distended intestine was found which ended abruptly with undistended gut following on. There was no mechanical obstruction. Post-operatively, because of distension, gastric suction and intravenous infusion were given. Four days later his condition had improved and he took feeds well. During the next few days he passed frequent, small, yellow, watery stools but then again became constipated. At 18 days the abdomen became very distended and he started to vomit copiously; an enema yielded some flatus only. He died at the age of 23 days. During the last three weeks of life he had daily enemata and stomach wash-outs, and was given 'amechol,' $\frac{1}{8}$ of a tablet, daily. Permission for post-mortem examination was not granted.

(4) Kathleen O'C. was born on September 2, 1942, following a normal pregnancy and delivery. She attended the Royal Liverpool Children's Hospital at the age of 2 years with a history of attacks of vomiting for three months. During the next six months she was admitted to hospital on several occasions with bouts of vomiting and abdominal distension, necessitating gastric suction and intravenous infusion. She was not seen again until she was 6 years old when she returned to the out-patient department with a history that for the last four years she had suffered from attacks of copious vomiting of green fluid every four or six weeks. Her bowels opened regularly. On examination the only abnormal finding was abdominal distension. All pathological investigations of blood, urine, stools, and duodenal juices were negative. A barium follow-through showed an enormously dilated coil of jejunum (Figs 6 and 7). For the next three months she was again in and out of hospital with attacks of distension and vomiting necessitating gastric suction and intravenous infusions. Several barium meals were given and always showed the same picture. At laparotomy the duodenum and first part of the jejunum were found to be enormously dilated, and the dilated intestine gradually tapered off into normal

FIG. 6.—Radiograph of Kathleen O'C. one hour after barium meal.

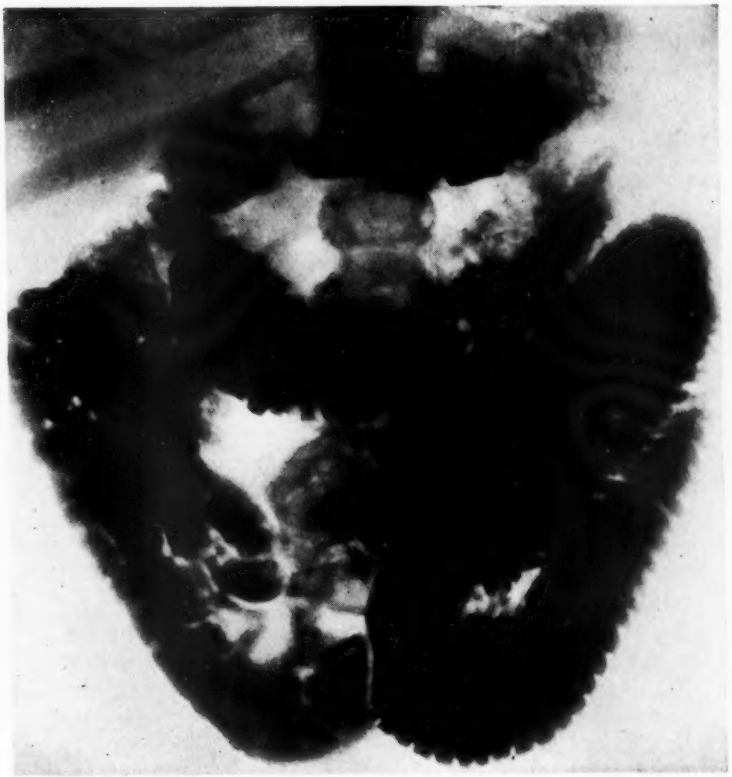

FIG. 7.—Radiograph of Kathleen O'C. three hours after barium meal.

bowel. There was no mechanical obstruction. From the date of operation there has been gradual improvement. The attacks of vomiting have become less forceful and frequent. Her bowels open regularly, but she still has a distended abdomen.

Very little is known about the family history of grandmother O'C., but it will be noted from the family tree that some of her brothers and sisters and some of her nephews and nieces, died of ' fits ' in infancy.

## Discussion

Ever since Hirschsprung in 1888 described the clinical syndrome which bears his name, the pathology of this condition has been under discussion. As early as 1901, Tittel noticed scantiness of ganglion cells in the myenteric plexus. Cameron, in 1928, discussing the aetiology of Hirschsprung's disease, described degeneration of ganglia in some sections, and Robertson and Kernohans (1938) recorded degeneration of the ganglion cells of Auerbach's plexus. Tiffin, Chandler, and Faber (1940), found localized absence of ganglion cells of the myenteric plexus in one case of congenital megacolon. The delay in recognizing the absence of myenteric ganglia as the major, if not the only significant pathological change in Hirschsprung's disease, was undoubtedly due to failure to differentiate clearly between cases of Hirschsprung's disease and other types of megacolon. Renewed interest in Hirschsprung's disease and its pathology date from 1948 when Swenson and Bill published the result of cases treated by recto-sigmoidectomy. Bodian, Stephens, and Ward (1949) have shown that in true Hirschsprung's disease the ganglion cells of Auerbach's plexus are absent from the rectum and usually from the lower sigmoid also.

Hirschsprung's disease is known to have an occasional familial basis; it is also occasionally diagnosed at birth or soon afterwards. Bodian *et al.* (1949) record three cases in the neonatal period and Perrot and Danon (1935) record another neonatal case. In these cases, however, the disease affected the rectum and sigmoid only and they were therefore capable of cure by recto-sigmoidectomy. Swenson (personal communication) has had several survivals following operation in the newborn. The cases reported here, however, differ from Hirschsprung's disease in the severity of the symptoms and the invariably fatal outcome.

Interest in functional intestinal obstruction of the newborn was awakened by the McG. family with its extraordinary familial incidence. However, in retrospect we believe that other cases presenting as lower small bowel obstruction in newborn babies, in which laparotomy and radiological investigations have failed to reveal a cause, have probably been of the same nature. Further, it seems probable that this condition is not uncommon. These cases are likely to remain unpublished, as surgeons are obviously reluctant to publish cases where the findings at laparotomy are so unsatisfactory. Necropsy also will be uninformative unless microscopic examination by serial sections of the gut is undertaken.

**Aetiology.** We have shown that in our case the myenteric ganglia were absent from the greater part of the large bowel. It is now well known that these changes are observed in the rectum or recto-sigmoid junction in cases of classical Hirschsprung's disease. The case here described thus appears to have the same aetiology as Hirschsprung's disease but differs in that a much greater segment of bowel was affected. It is current teaching that preganglionic vagal and parasympathetic nerve fibres end as arborizations around neurons of the myenteric plexus and that local intestinal reflex movements are initiated and controlled through neurons in this plexus. In the absence of these nerve cells the affected segment is deprived of both parasympathetic innervation and local reflexes, with resultant absence of peristalsis. Attempts by the normally innervated proximal intestine to push the bowel contents past the inert segment appear to be responsible for the muscular hypertrophy usually observed in Hirschsprung's disease. No such hypertrophy was observed in our case, presumably because the child did not live long enough. Zuelzer and Wilson (1948) have demonstrated that hypertrophy is roughly proportional to the time of survival.

Cameron (1928) suggested that the absence of the myenteric ganglia could be attributed to inflammation. We suggest that the occasional familial incidence of this condition, as exemplified in the McG. family and the family quoted by Zuelzer and Wilson (1948), favours a congenital abnormality of the neuro-muscular mechanism, probably a neural agenesis.

A point of interest is the presence of the ganglia in approximately the area supplied by the vagus and their absence from that supplied by the sacral outflow. We were, however, not able to determine the exact distribution of the vagus and sacral nerves to the large bowel and the matter therefore remains speculative.

It is difficult to resist the inference that Kathleen O'C. suffered from the same condition in a segment of the jejunum. If she suffered from the same type of condition at a higher level, then it must be assumed that in a proportion of these cases the affected segment will not include the most distal bowel. Such cases would be amenable to treatment by excision or short-circuiting operations. Swenson (personal communication) has had a patient with

segmental affection of the ileum, cured by excision of the segment. On section the excised part of the ileum showed absence of ganglion cells of the myenteric plexus.

Although Kathleen had recurrent attacks of vomiting, obstruction never became absolute and the child survived. It seems possible that the difference in the site of the lesion explains the difference in prognosis. The area of inert bowel may possibly not present the same resistance to fluid as to solid intestinal contents.

We believe it to be the first time that this clinical syndrome has been described in at least two successive generations. We should add that intestinal radiographs of Michael McG's mother were normal.

**Treatment.** It seems probable that in the future these children will be submitted to laparatomy. At the time of operation a rough estimate of the level of agenesis of ganglion cells can be made by observing the level of dilated and non-dilated bowel. In cases where the descending colon only is affected, a transverse colostomy appears to be justifiable. In cases of involvement proximal to the middle of the transverse colon, an ileostomy or caecostomy is feasible. Babies stand all types of enterostomy badly; even transverse colostomy may be poorly tolerated. When we operated upon Michael McG. we believed that an ileostomy would lead to rapid death from dehydration, but we have since heard that Swenson (personal communication) has in fact been able to perform a successful terminal ileostomy in one of these cases.

**Summary**

Functional intestinal obstruction of the newborn affecting several members of one family is described. The possible relationship of this condition to Hirschsprung's disease and the treatment are discussed. We suggest that functional intestinal obstruction in the newborn, with or without a familial basis, is a definite clinical and pathological entity.

We should like to thank Professor Norman B. Capon for referring Michael and Anthony McG. and Kathleen O'C. to us, and Mr. Philip H. Hawe for permission to record the case of Patricia McG. Our thanks are also due to Miss J. Henderson who prepared the histological material.

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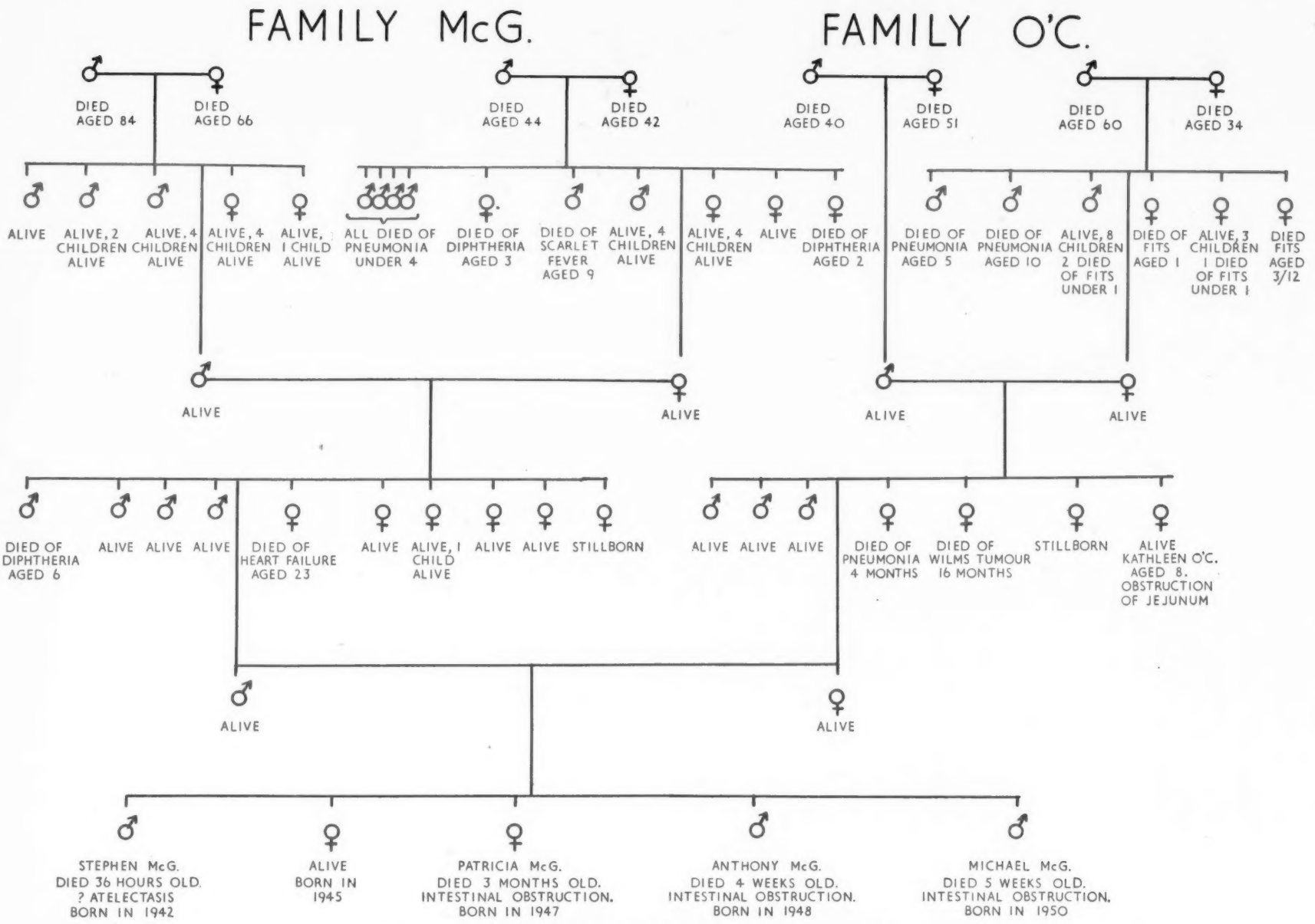


FIG. 8.—Family tree of Michael McG. referred to on page 296.

# A CASE OF TROPICAL EOSINOPHILIA AND ACUTE NEPHRITIS

BY

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(Received for Publication August 21, 1950)

Renal lesions have not been described in any of the cases of tropical eosinophilia so far reported.

This paper describes an attack of acute nephritis during the course of tropical eosinophilia.

### Case Report

J.H. was a girl of 6 years who was admitted to St. James's Hospital, Leeds, on January 11, 1947, because of swelling of the face and albuminuria.

The child was well until January 6, 1947, when she developed a cough. Five days later her face and legs became swollen.

She had had measles and mumps in infancy, but no other illnesses. Two years previously she had come to Britain from India where she was born. She had suffered from 'wheezing' attacks for two years.

There was no history of worm infestation or any tropical infection.

The father was British and had been killed in action, and the stepfather was also British. The mother said that she and all her forebears were British. She was healthy, but had an illness diagnosed as 'chyluria' in July, 1947, which, it was assumed, was due to filariasis, although the parasite was never isolated.

On admission it was seen that the oedema had subsided, but there was a trace of albumin and scanty red cells in the urine. The child was discharged after 10 days in hospital, but five weeks later developed a painful cough and fever and was readmitted on March 26.

There was a large quantity of albumin in the urine at this time, and a few red cells on microscopical examination. Scattered râles were present in the chest. She was again discharged on May 30, but three days later developed generalized oedema and albuminuria accompanied by mild bronchitis, and was readmitted on June 4. Widespread rhonchi and râles were present in the chest. A blood count showed marked eosinophilia. A radiograph of the chest revealed scattered mottling described by the radiologist as 'coarsening of the lung mesh.'

The urine gradually returned to normal, but otherwise the child's condition remained virtually unchanged with a constant eosinophilia (see Table 1) until July 29, when 0·1 g. of N.A.B. was given followed by six injections of 0·1 g. at weekly intervals. From this time there was a steady improvement in the clinical condition. The eosinophilia had disappeared by August 28. The blood sedimentation rate (Westergren) fell from 58 mm. on May 28 to 1 mm. on July 30.

Re-examination two years later, on June 9, 1949,

TABLE 1
DIFFERENTIAL COUNT

| Date | Total White Blood Cell Count (per c.mm.) | Neutrophils (%) | Eosinophils (%) | Lymphocytes (%) | Large Monocytes (%) | Smear Cells (%) | Basophils (%) |
|---|---|---|---|---|---|---|---|
| 18.6.47 | 20,300 | 13·5 (27,400) | 50·0 (10,150) | 29·0 (5,887) | 1·5 (305) | 5·0 | 1·0 (203) |
| 2.7.47 | 22,400 | 19·5 | 39·5 | 36·5 | 1·5 | | 3·0 |
| 24.7.47 | 23,400 | 31·0 | 41·0 | 26·0 | 2·0 | | — |
| 29.7.47 | N.A.B. treatment started | | | | | | |
| | 16,700 | 33·0 | 40·0 | 24·0 | 2·0 | | 1·0 |
| 4.8.47 | 14,700 | 31·0 | 30·0 | 38·0 | | | 1·0 |
| 15.8.47 | 13,400 | 49·0 | 23·0 | 22·0 | 4·0 | | 2·0 |
| 23.8.47 | 14,000 | 55·0 | 15·0 | 27·0 | 2·0 | | 1·0 |
| 29.8.47 | 9,000 | 50·0 | 6·0 | 40·0 | 3·0 | | 1·0 |
| 5.9.47 | 9,600 | 35·0 | 3·0 | 52·0 | 7·0 | | 3·0 |
| 9.6.49 | 6,500 | 48·0 | 5·0 | 44·0 | 3·0 | | |

Dosage of N.A.B. was six injections each of 0·1 g.



FIG. 8.—Family tree of Michael McG. referred to on page 296.

revealed no evidence of disease clinically or radiologically and the blood picture was normal.

**Investigations.** The following results were obtained during the periods in hospital.

The blood count is set out in Table 1.

Blood pressure on June 16, 1947, was 110/70.

Sputum was examined on July 3, 4, 7, and 24, 1947, when no tubercle bacilli, mites, or eosinophils were present.

The Wassermann reaction was negative on July 11, 1947.

Stools were examined on June 19 and 28 and no parasites or ova were found.

The tuberculin reaction on May 6, 1947 (1/1,000 O.T.) was negative.

Urine analysis on several occasions gave the following results.

| Date | Albumin | Casts | R.B.C. |
|---|---|---|---|
| 18.6.47 | + | Hyaline | Occasional |
| 23.7.47 | Trace | — | — |
| 10.9.47 | — | — | — |
| 9.6.49 | — | — | — |

B.S.R. (Westergren) readings were

| | | |
|---|---|---|
| 28.5.47. | 58 mm. in 1 hour. | 100 mm. in 2 hours |
| 23.7.47. | 46 mm. in 1 hour. | 80 mm. in 2 hours |
| 30.7.47. | 1 mm. in 1 hour. | 3 mm. in 2 hours |

A radiograph on June 19, 1947, showed an appearance of the lung fields indicating vascular engorgement, the features of which are enlargement of the root vessels with symmetrical coarsening of the lung mesh. Later radiographs (September 4) showed 'considerable reduction in pulmonary hyperaemia, now only increased in posterior and midbasic vessels,' and on September 24, 'marked improvement, increased vascularity of the lung mesh persists'; finally, on June 10, 1949, it was reported that 'the heart and lungs are now normal.'

A biopsy report on a gland from the left axilla and a portion of muscle from the left deltoid (Professor C. J. Polson, then pathologist at St. James's Hospital) stated:

> 'Some of the vessels in the small lymph gland submitted contain a distinct excess of eosinophil polymorphs and here and there through the gland itself there are a number of eosinophils, and there is some histiocytic reaction. There is no evidence that this is Hodgkin's disease. The appearances are compatible with a parasitic infestation in the neighbourhood. Neither the lymph gland nor the small portion of striped muscle which accompanies it show evidence which would permit a diagnosis of periarteritis nodosa. It would appear that there is a distinct excess of eosinophils in the circulating blood.'

## Discussion

Eosinophil counts of the height described are seldom seen apart from the condition known as tropical eosinophilia.

Frimodt-Möller and Barton (1940), and Weingarten (1943) independently described a condition seen in India resembling pulmonary tuberculosis in its insidious febrile onset, x-ray appearances, and wasting progress. Asthma was frequently present, very high eosinophilia was the rule, and, as Weingarten showed, arsenic was a specific cure. The x-ray appearances resembled those of miliary tuberculosis, a diffuse mottling of all parts of the lung being present.

There are numerous case reports in the literature, chiefly from India, but also from Africa and Australia. Those from Britain were all of persons recently returned from the tropics (Apley and Grant, 1944, 1945; Lal, 1945; Treu, 1943, 1944; Irwin, 1946; Stephan, 1946; Simeons, 1943; Hodes and Wood, 1945; Chaudhuri, 1943; and Parsons-Smith, 1944).

Clinically, in addition to the signs in the chest, the spleen and glands may be enlarged, but no mention is made of involvement of the kidneys or any other organ. The disease does not tend to wax and wane in severity, and spontaneous recovery usually occurs after a long time without treatment.

The aetiology is obscure, but has been attributed to tyroglyphid mites found in the sputum (Carter, Wedd, and D'Abrera, 1944; Carter and D'Abrera, 1946a and b; Soysa, 1949; Hall, 1946). The Wassermann reaction may be positive and the Kahn weakly positive (Menon, 1945; Greval, 1940; D'Abrera and Stork, 1946).

All age groups may be affected (Viswanathan, 1948).

**Differential Diagnosis.** The present case thus shows many features of tropical eosinophilia, namely chronicity, high, persistent eosinophilia, asthmatic bronchitis, x-ray changes, and response to arsenic. Also the patient had lived in the tropics. The haematuria could be explained as an unrelated event.

The condition differs from periarteritis nodosa in several respects. The course of the tropical disease is less severe and fulminating. The x-ray changes are diffuse and not distributed along the lung arteries (Elkeles and Glynn, 1944; Harris, Lynch, and O'Hare, 1939). The eosinophilia is higher than that usually seen in periarteritis nodosa (Rich, 1942; Tisell, 1941; Harkavy, 1941; Lovshin and Kernohan, 1948); and the response to arsenic does not occur in that condition. Haematuria can occur in periarteritis but oedema is rare (Mayo Clinic Symposium, 1949). Löffler's syndrome (Löffler, 1932), or eosinophilic pneumonia is a much milder and more transitory disease. The eosinophilia is not great and the lung changes are transitory localized opacities, never a diffuse mottling. The

conclusion reached was that the patient had been suffering from tropical eosinophilia contracted in India, and that acute nephritis developed on her arrival in Britain. Whether this was precipitated by the climatic change, and whether the tropical eosinophilia was a factor in its development, are questions we are unable to answer.

**Summary**

A case with gross eosinophilia, asthmatic bronchitis, and acute nephritis is described. The patient had recently returned from India.

Our thanks are due to Professor W. S. Craig for permission to publish this case and for much valuable advice. We are indebted to Professor C. J. Polson for the biopsy report, Dr. J. Wall and Dr. C. Pickard for the radiological reports, and to Dr. W. McIntosh for access to the case records.

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# CONGENITAL MITRAL STENOSIS

BY

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Two cases of isolated congenital mitral stenosis are presented, because of the great rarity of the condition when properly authenticated by post-mortem examination, the doubts about its aetiology, and the difficulty of making a clinical diagnosis.

## Case Reports

**Case 1.** The patient, a girl and an only child, was admitted at the age of 2 years 6 months with a history of cough, wheezing, and dyspnoea for six months. Previously she had been perfectly well with no history of cyanosis. She was found to have signs of a right basal pleural effusion. There was no cyanosis and no clubbing of the fingers, and no other abnormal physical signs were found. A chest radiograph showed an effusion, collapse of the right middle lobe, and a general non-specific increase of lung markings. The intradermal tuberculin test to a strength of 1 mg. was negative, and the diagnosis made was simple pleural effusion of unknown origin. The effusion persisted, but she remained fairly well for the next four months. She then developed severe dyspnoea, pitting oedema over the sacrum, distension of the neck veins, and enlargement of the liver to the umbilicus. The clinical diagnosis was changed to that of congestive heart failure of unknown aetiology. At no time were any abnormal physical signs found in the heart. No murmurs were heard. The blood pressure was 125/90. She was given digitalis and a low sodium diet, but failed to respond to treatment and died six months after admission, at the age of 3 years.

The pleural effusion was aspirated on three occasions, 200 ml. straw-coloured fluid being withdrawn on the first occasion, 580 ml. on the second, and 130 ml. on the last.

SPECIAL INVESTIGATIONS. There was no apparent cardiac enlargement on radiography.

The pleural fluid contained an equal mixture of mononuclear and polymorphonuclear leucocytes, and was sterile on culture. There were elastic fibres and bacilli, mostly Gram-negative, in the sputum.

The urine had a trace of albumin, and a few red cells in a centrifuged deposit.

The Wassermann reaction was negative.

A blood count gave Hb. 10 g. %, and R.B.C.s 4·3 m. per c.mm.

There was nothing of note in the pregnancy history.

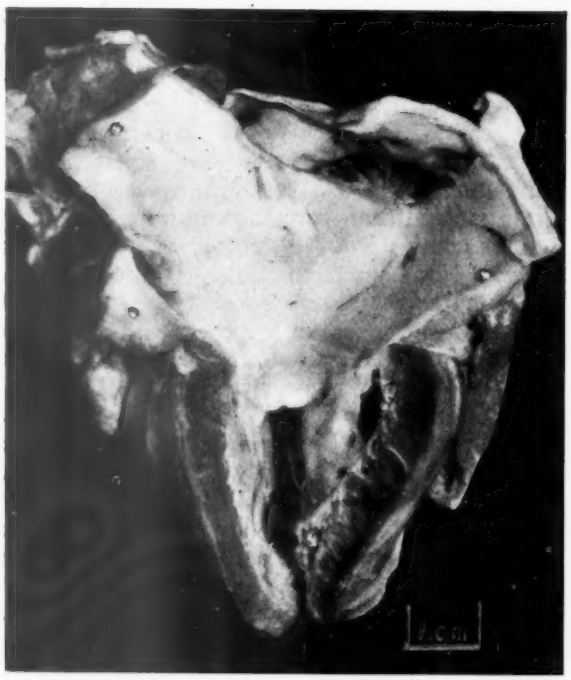
NECROPSY. The gross naked eye appearance of the body cavities and organs was of chronic venous congestion. There was a bilateral pleural effusion with adhesions on the right side.

The heart (Fig. 1) weighed 90 g. (normal for age of child 57 g., Coppoletta and Wolbach, 1933). The right auricle appeared normal and was 1-1·5 mm. thick. The tricuspid valve had a margin of 62 mm. and showed no thickening. The right ventricle was 3 mm. thick and the pulmonary valve (margin 30 mm. in circumference) also appeared normal. The left auricle was enlarged, the endocardium pale, the muscle 3 mm. thick. The mitral valve was thick and rigid, the margin being 30 mm. The left ventricle did not appear enlarged; the muscle was 5-7·5 mm. thick. The aortic valve appeared normal, with a margin of 31 mm. The foramen ovale and ductus arteriosus were completely obliterated. The aorta and great vessels appeared normal.

On microscopy, the thickened endocardium, the mitral valve and the bands of the tissue extending into the heart muscle were seen to consist of collagenous tissue varying from loose fibrillary to a dense, almost cartilaginous structure. No foci of cellular infiltration or Aschoff nodes could be found either amongst the fibrous tissue or in any sections of the heart muscle, including the interventricular septum. The coronary vessels were normal and there were few vessels in the connective tissue of the stenosed valve and auricular endocardium. The diaphragm and pericardium showed an increase in collagenous tissue but no evidence of inflammatory change. In the lung almost all the alveoli had large numbers of haemosiderin-containing phagocytes. Small areas of bronchopneumonia were present. Other organs showed no lesions other than venous congestion.

**Case 2.** The patient, a girl, was admitted at the age of 17 months with a history that until two weeks previously she had been perfectly well. She then developed a cough and fever, her respirations became rapid, her alae nasi were working, and she was generally poorly. She vomited two days before admission.

On admission she was acutely ill, with dyspnoea, cyanosis, and signs of extensive bronchopneumonia (pulse 160, temperature 102°, and respirations about 60 per minute). There was a triple rhythm at the cardiac apex, but at that time, probably owing to the high respiration rate and gross signs in the chest, no murmur was heard. The tip of the spleen was felt. There was no clubbing of the fingers. A diagnosis of bronchopneumonia was made and confirmed radiologically.


FIGS. 1 and 2.—Photographs of the left side of the heart showing pale thickened endocardium in a dilated auricle, thickening of the mitral valve and short thick chordae tendineae. Pale strands of fibrous tissue may also be seen penetrating the ventricular muscle.

She was treated with sulphamezathine and aluminium procaine penicillin and in four days was greatly improved and the cyanosis had disappeared. Seven days later she had a relapse, and the findings were similar to those in the first attack. This time two murmurs were heard at the apex, and there was some disagreement as to which of the two, systolic or diastolic, was the louder. The phonocardiogram showed that the diastolic murmur was louder than the systolic. The liver was enlarged, reaching to the umbilicus, and the veins of the neck were engorged. Congestive heart failure with superimposed bronchopneumonia was diagnosed, and it was thought that the probable cause was congenital mitral stenosis. The question of superimposed subacute bacterial endocarditis was considered, and penicillin was given, but the blood culture was negative. She was given digitalis, and made considerable improvement in four or five days, the temperature again subsiding to normal. She relapsed a month after admission and died.

SPECIAL INVESTIGATIONS. An intradermal Mantoux test (0·1 mg.) was negative.

A radiograph of the chest showed signs which, it was thought, were due partly to pulmonary congestion and partly to superimposed bronchopneumonia. There was no apparent cardiac enlargement until a few days before death.

The urine was normal.

An E.C.G. showed a moderate right axis deviation.

A blood count gave Hb. 9·6 g. %, R.B.C.s 3·8 m. per c.mm.

A postnasal swab gave a coagulase positive culture of *Staph. aureus*.

Pregnancy had been uneventful. There was no evidence of any infection.

NECROPSY. The body was that of a well nourished female child. There was no generalized oedema. Both pleural cavities contained small amounts of straw-coloured fluid. The lungs were heavy and deep red, the right lower lobe having an area of fibrinous pleurisy.

The heart (82 g., normal for age 45 g.) had a small, pale area of fibrous tissue over the anterior aspect of the apex of the right ventricle (Fig. 2). The right auricle was normal, the tricuspid valve, with a margin of 57 mm., appeared normal. The right ventricle was 4 mm. thick and its cavity was normal. The pulmonary valve was normal (margin 35 mm.). The left auricle was increased in size, the wall measuring 2-4 mm. in thickness, lined by a pale fibrous layer 0·5-1 mm. thick. The mitral valve cusps were pale, thickened and rigid, the circumference of aperture being 25 mm. The left ventricle appeared of normal size, 7-8 mm. thick. There were pale areas in the muscle, particularly in the papillae leading to the mitral valve. The aortic valve had a thickened edge, maximal at the mid-portion of each cusp, the bases being relatively normal. . The internal circumference was 28 mm. The coronary arteries were normal. The foramen ovale was completely obliterated. The ductus was just patent, with a circumference of about 2 mm. The great vessels appeared normal. Histologically the heart showed lesions very similar to those in case 1, the only difference being that the areas of fibrosis corresponding to the pale areas seen by the

naked eye were smaller but more widely scattered. No vascular or inflammatory lesions could be found. The lungs did not show pneumonia, but the alveoli contained large numbers of haemosiderin-laden macrophages. The diaphragm and pericardium showed a general increase in connective tissue, but no inflammatory changes. Other organs showed no lesions other than venous congestion.

**Summary of Cases.** Both of these children died with venous congestion as the major presenting feature.

The gross anatomical lesion in the heart consisted of mitral stenosis with fixation of the valves, an increase in fibrous tissue throughout the left auricle, and areas of fibrosis in the left ventricle. In one case there was a slight increase in the connective tissue of the aortic valve. The foramen ovale in both instances was completely obliterated and there was no defect in the inter-auricular or ventricular septa.

Histologically the fibrous tissue was avascular. There was no associated inflammatory reaction and no Aschoff tissue could be found.

## Discussion

Taussig (1947) aptly summarizes the present state of our knowledge of such cases:

> 'Not uncommonly autopsy reveals a condition in which it is wellnigh impossible to determine whether the abnormality in the mitral valve was due to a congenital malformation or to an acquired rheumatic infection.'

There are three well accepted causes of cardiac lesions in very young children: (1) congenital deformity; (2) foetal endocarditis; (3) infantile rheumatic heart disease.

The nature of a congenital deformity of the heart depends largely upon the stage in development at which the abnormality begins. In the case of mitral atresia with septal defect the abnormal growth must begin before the complete formation of the septum. If, however, the abnormal growth begins after the fourth month the septa would be intact and mitral stenosis anatomically similar to the adult disease could occur. The complete closure of the foramen ovale in these cases at first sight appears to be the shutting of a convenient shunt, but the foramen acts as a valve facilitating blood flow from right to left and only if the obliterating fold is incomplete does it enable blood to flow from left to right. An increased pressure in the left auricle is likely to keep the foramen permanently closed.

Valvular lesions in neonatal hearts are mostly ascribed to foetal endocarditis. Farber and Hubbard (1933) found ten such cases in the literature and added four of their own. They appear to consider the presence of fibrosis and calcification as sufficient evidence for their inflammatory origin, though two of their own cases showed other signs of inflammation. Gross (1941), in a critical discussion and review of so-called foetal endocarditis, regards the concept as untenable. He draws attention to the absence of inflammatory change in reports of these cases, and to the similarity of the myocardial lesions to healed bland infarcts due to vascular occlusion. A large number of foetal deaths are associated with cardiac abnormalities, and it seems surprising, if foetal endocarditis does occur apart from congenital syphilis, that there is such an extreme dearth of reports of active endocarditis in foetal hearts. We, in fact, are not acquainted with any such report. The increased connective tissue in these abnormal hearts appears to be normal tissue but in abnormal amounts, and it gives little support to the theory of foetal endocarditis. The evidence is completely circumstantial and negative, and one can hardly help but conclude that the lesions are congenital in origin, and analogous to other congenital deformities of the heart, in which abnormal growth begins relatively late in the heart's development.

There have been several reports of rheumatic carditis in infants (Kissane and Koons, 1933; Ferguson, 1893; McIntosh and Wood, 1935; Eigen, 1938). McIntosh and Wood showed, from a combination of figures from various workers, that 1·3% of 2,884 cases of rheumatic fever occurred in the first three years of life. They described 24 cases of their own in which the disease occurred in the first two years with necropsy findings in six, in all of which hyaline degeneration and Aschoff tissue was found. Eigen's case, an infant 2 years old, showed the characteristic histological features of rheumatic heart disease, with areas of cellular infiltration and necrosis with giant cells.

In an analysis of 1,700 children with rheumatism Walsh, Bland, and Jones (1940) found that the minimum time for the development of mitral stenosis was three years and in only five of their 48 cases of mitral stenosis did the lesion develop in five years from the onset of recognizable disease. If the infants under the age of 2 dying with mitral stenosis had had rheumatic disease of the heart, the process must have been uncommonly rapid and complete to have produced the lesion and for it to have become completely scarred and inactive. The children who have died with known rheumatic heart disease in this age period have shown histological evidence of rheumatism. The valvular and endocardial lesions in rheumatic heart disease characteristically show a permanent increased vascularity (Koletsky, 1946), whereas the valvular and endocardial lesion in the two cases of mitral stenosis that we have examined do not show such change.

It is felt, that whilst acute rheumatism does occur

in children under the age of 3, the presence of fibrosis in the heart in areas frequently affected by rheumatic scarring later in life does not constitute a proof of the rheumatic aetiology of the infantile lesions.

Mitral stenosis is much less common in infantile deformities of the heart than in mitral atresia, Manhoff and Howe listing 28 cases of atresia in 1945. Mitral atresia is usually associated with gross deformity of the heart and with auricular septal defect, but cases of mitral stenosis, such as the two cases here described, form a small group of heart deformities in which the mitral valve is affected alone, or with deformity of the aortic valve, and without any defect in the auricular or ventricular septa. Such cases of mitral stenosis without septal defects, and confirmed by necropsy, have been described by Day (1932), Johnson and Lewes (1945), McConnell (1950), Eigen (1938), and Newns (1938). The cases described by the first three authors showed a histological picture similar to our cases —an increase of connective tissue without inflammatory change—and our argument, suggesting a developmental abnormality, applies in their cases as in our two cases. Eigen's case has already been mentioned. There is no mention of the histology in Newns' case.

The clinical picture in case 1 was particularly confusing owing to the absence of cardiac murmurs. It is known that such a difficulty may arise in mitral stenosis.

**Summary**

Two cases of congenital mitral stenosis are described.

One presented for four months as a right basal pleural effusion, and had no cardiac murmurs at any stage. The clinical diagnosis was then changed to one of congestive heart failure of unknown aetiology. The second presented as broncho-pneumonia superimposed on congestive heart failure, and the characteristic murmur was found. Death in each case was due to congestive heart failure.

The lesions in the heart appeared to be congenital in origin and due to abnormal development after the cavities of the heart had been fully formed. No evidence of foetal endocarditis or of a rheumatic process could be found.

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# SARCOMA OF THE HEART IN A CHILD

BY

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Malignant heart tumours are rare, and seldom diagnosed during life; such a diagnosis is particularly difficult in childhood. Mahaim (1945), in a comprehensive review of over 400 heart tumours, found 87 primary sarcomas, only five of which occurred in children under 15 years. Lisa, Hirschhorn, and Hart (1941), reviewing the literature, found 30 reported cases of secondary tumour involvement of the heart with only two examples of sarcoma in childhood.

This case is reported principally on account of the unusual presentation and because of the difficulty in making a clinical diagnosis. The prospects of successful cardiac surgery (Beck, 1942) now cause clinical diagnosis to be of more than academic interest.

### Case Report

T.W., a boy of 3 years, complained of sudden pain in the right hip joint, associated with fever and general malaise. A radiograph of the pelvis taken a week after the onset seemed normal, but he was treated intensively with systemic penicillin on the assumption that his condition might be acute osteomyelitis. The fever subsided after four days, but because of a limp and a rapid general deterioration during this period he was admitted to hospital. The history revealed that the milestones of development had been greatly delayed, and that recently he had exhibited choreiform movements with a tendency to fall.

The child was pale and wasted, making grunting noises, and displaying involuntary movements of hands and face. The temperature was 100° F., the pulse 150 per minute, and respiration 35 per minute.

He seemed in obvious pain, though the site was difficult to determine because of his mental backwardness. The right hip joint movements were all limited and painful in extreme ranges, but there was no localized bony tenderness. The fundi were normal, and there were no neurological signs, apart from the choreiform movements.

He had a regular pulse, persistently over 130 per minute. The blood pressure was 105/70 mm. Hg. The neck veins were prominent. An apex beat in the fifth left space 4 in. from the mid-sternal line was localized, and dyspnoea was easily induced. The heart sounds were faint, but a soft apical systolic murmur was detected. An E.C.G. showed right ventricular preponderance and no evidence of heart block. Cardioscopy indicated general heart enlargement only, and a chest radiograph did not suggest lung pathology in this initial phase. The blood count was normal and repeated blood cultures were negative.

A radiograph of the pelvis now showed extensive erosion of the right iliac and pubic bones, as well as of the upper ends of both femora. The E.S.R. was 50 mm./hr. and the Mantoux reaction (1/100) negative.

Treatment with penicillin, aspirin, and phenobarbitone did not influence the fever or the rapidly deteriorating clinical condition, and three weeks after admission he developed facial oedema, cyanosis, congested neck veins and a basal pericardial friction rub. The liver could be felt two fingers' breadth below the right costal margin; coarse rhonchi were audible over both lungs. A radiograph of the chest three days before death showed generalized lung mottling with a distorted right heart shadow. Breathing became embarrassed, and cyanosis deepened before death, five weeks after the onset of symptoms.

**Differential Diagnosis.** When the boy was first seen it seemed possible that this might be a case of rheumatic chorea with carditis, complicated by osteomyelitis. The involuntary movements, tachycardia, and uncontrollable fever with hip pain favoured this impression, but his mental state made it difficult to get a clear picture.

The discovery of disseminated bone lesions made us entertain the possibility of *Bact. coli* endocarditis with migrating osteomyelitis, though this was difficult to correlate with the other findings.

When superior vena caval block and generalized mottling of the lung fields became evident terminally, sarcomatosis with a mediastinal deposit was postulated. The cardiac signs might then be explained by neoplastic involvement, though the improbability of heart tumour at this age made us tentatively venture the diagnosis of rheumatic chorea and pancarditis, with osteomyelitis and terminal thrombosis of the superior vena cava.

**Necropsy Findings.** Externally the body was as described above. The heart was enlarged (weight, 210 g.), and the pericardium contained about 10 oz. of coloured fluid. There was a large tumour measuring $5 \times 4{\cdot}5 \times 5$ cm. in the position of the inter-auricular septum, almost filling the left auricle and obstructing the mitral valve orifice. It also bulged into the right auricle, particularly superiorly, and compressed the superior vena cava as it entered the auricle (Fig. 1).

The aorta, and to a less extent the pulmonary artery, were also compressed by the growth. It was covered by

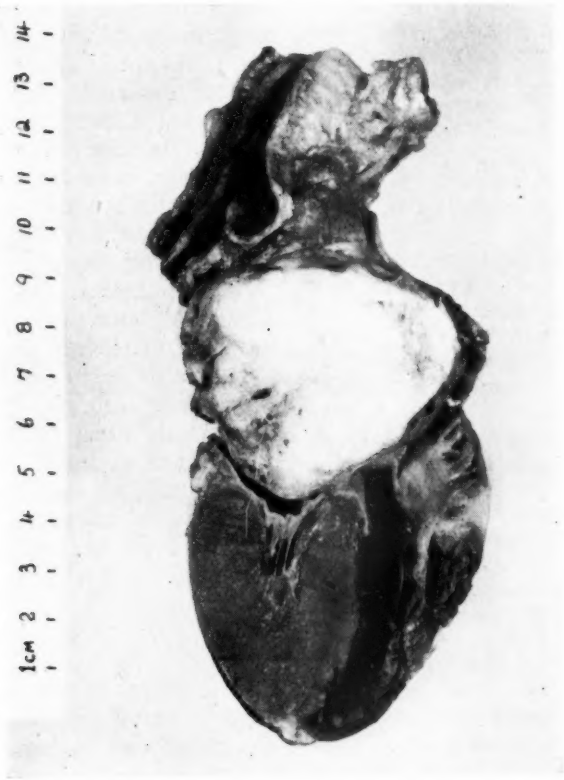

FIG. 1. Coronal section of heart showing tumour filling both auricles and compressing superior vena cava.

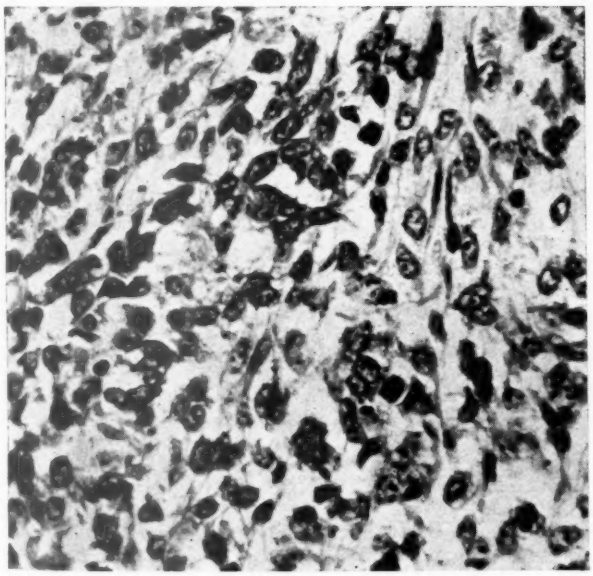

FIG. 2.—Photomicrograph showing structure of heart tumour (haematoxylin and eosin. ×380).

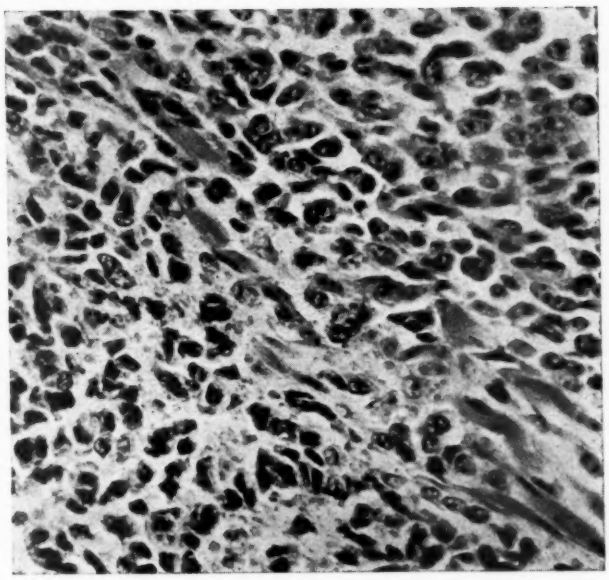

FIG. 3.—Photomicrograph showing infiltration of gluteus muscle by tumour of right ilium (haematoxylin and eosin. ×360).

endocardium except at its widest part, where the surface was roughened with loss of endothelial covering. The cut surface of the tumour showed it to be homogeneous and white. There was a tumour deposit about 1·5 cm. in diameter in the wall of the left ventricle posteriorly and numerous small nodules on the aorta and pulmonary artery.

Each pleural cavity contained about 20-30 oz. of straw-coloured fluid. There were numerous pale tumour nodules (varying from 1 mm. to 1 cm. in diameter) on the pleural surfaces of both lungs giving them a striking resemblance to a 'hobnailed' liver. The cut surface showed similar nodules scattered uniformly throughout the lung substance. The right lobe of the liver contained a few pale tumour deposits, and there was a solitary nodule 0·75 cm. in diameter in the cortex of the right kidney.

White tumour tissue was found in the head of the left femur and the right ilium. The right gluteus externally, and the iliacus internally, were partially replaced by firm growth. The mesenteric, para-aortic, and cervical nodes were enlarged, firm and uniformly white, due to replacement by neoplasm.

There were two small cavities in the region of the right basal ganglia about 0·5 cm. in diameter containing clear fluid.

All other organs appeared normal.

When the tumour nodules were microscopically examined they were all very similar, consisting of spindle-shaped cells running in bundles, between which there were collagen fibres. The appearance was that of a fibrosarcoma.

There was no evidence of rheumatic infection of the heart, and the basal ganglia cavities seemed to be long standing developmental cysts. There was no evidence of chronic venous congestion. No tumour emboli or ante-mortem thrombi could be found in the vessels of the brain.

## Discussion

The diagnosis of heart tumours during life is difficult, but certain features aiding ante-mortem recognition have been discussed at length by Yater (1931). A perusal of the literature seems to indicate that the important criteria for considering the diagnosis are intractable cardiac failure with no obvious cause; inconstant cardiac arrhythmias, e.g. heart block; evidence of valvular lesions influenced by posture; rare stenotic lesions, viz. tricuspid stenosis and acquired pulmonary stenosis; haemorrhagic pericardial effusion; evidence of obstruction to the major thoracic vessels; of a tumour elsewhere with cardiac dysfunction; unusual cardiac configuration on cardioscopy; and, in children, the presence of associated developmental abnormalities in a suspect case, particularly tuberose sclerosis.

Not many of these features may be expected in one case and bizarre combinations occur (Mahaim, 1945). In the child under discussion the combination of superior vena caval block, wasting, late pericardial friction rub, cardiomegaly, persistent tachycardia, and a changing systolic murmur with evidence of bone tumours, in retrospect suggested the correct diagnosis.

In this case it is difficult to be sure whether the heart tumour was primary or secondary. On the unreliable criterion of size it was primary. As sarcoma of bone rarely metastasizes to other bones, the multiple skeletal involvement in this case also suggested the heart as the primary site. The onset with a painful limp, however, might indicate that the primary tumour was in the right ilium which was the next largest tumour mass.

With such a large mass encroaching on the left auricle and mitral orifice, it is remarkable that there were no signs of congestive heart failure or mitral lesion during life. However, other observers have commented upon the surprising size reached by some cardiac tumours before obvious signs develop (Reisinger, Pekin, and Blumenthal, 1942). The E.C.G. finding in this case is understandable, as no deposits were found in any situation likely to affect the conducting system, and the deposits in the ventricles were relatively small.

It is difficult to explain the involuntary movements that were so prominent a feature throughout the illness. The cysts were considered on microscopic evidence to be developmental, and not embolic softenings as might be expected in view of the roughened surface of the main tumour.

## Summary

A case of fibrosarcoma of the heart, probably primary, with involvement of bones, lung, and other organs is described in a child aged 3.

We wish to thank Professor A. G. Watkins and Professor J. Gough for their helpful criticism and advice. We are also indebted to Mr. H. A. Griffiths for the photograph.

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# THE Q-T INTERVAL IN RHEUMATIC FEVER

BY

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The prolongation of the Q-T interval in the electrocardiogram of patients suffering from valvular disease or rheumatic carditis was noticed by Berliner (1931) and by Drawe, Hafkesbring, and Ashman (1937). These observations were not considered to be of value for the diagnosis of cardiac involvement during or after an attack of acute rheumatic fever until Taran and Szilagyi (1947), studying a series of 50 cases, claimed that the duration of electrical systole was lengthened in all children whose electrocardiograms had been taken during an attack of acute rheumatic carditis.

Their report revived interest in the value of the measurement of the Q-T interval, and further papers have since been published. Abrahams (1949) found a prolonged Q-T interval in 90 of his 100 patients with active carditis, and agreed with Taran and Szilagyi (1947) that this measurement was of diagnostic value. However in Pokress' and Goldberger's (1949) series only 14 of the 50 patients (28%) with active rheumatic fever had a Q-T interval above the normal maximal value.

The results of the present series differ significantly from those of Taran and Szilagyi (1947) and of Abrahams (1949). This paper* is an attempt to explain this difference, and to assess the value of the measurement of the Q-T interval in rheumatic fever.

## Methods

Goldberger's (1948) nomogram was chosen to relate the measured Q-T interval to the heart rate. This nomogram expresses the Q-T interval as the ratio of the measured to the ideal interval for that heart rate. The ideal Q-T interval for each heart rate is estimated by the use of Bazett's (1920) formula, and since this formula was used in the other reports, we were able to compare our results with those of the earlier workers.

All recordings were made with the child in a reclining posture, and after he had been in bed for at least 24 hours. In approximately half the cases the apparatus used was the General Electric Company electrocardiographic machine, and in the rest the Elmquist Junior (General Radiological Company) machine.

Lead II was used for the measurements, unless the end of the T wave was ill defined, in which case the complexes in lead I or lead III were preferred. The measurements were made with a pair of compass dividers and a hand lens. Particular care was taken while measuring the Q-T interval to measure it from the beginning of the Q deviation to the point at which the T wave again became isoelectric. The Q-T and R-R intervals of at least five cardiac cycles were measured, and the Q-T ratio of each separate cycle was found on the nomogram and the average of these values estimated.

## Material

One hundred and twelve electrocardiograms of 102 children, whose ages ranged from $3\frac{1}{2}$ to 14 years, were examined. All the children were in-patients at the Children's Hospital, Sheffield, and at the Ash House Hospital School. Eighty-two had rheumatic fever at various stages, and the remaining 20 were controls. They were divided into the following groups.

**Group I.** These children had definite evidence of active rheumatic infection. Polyarthritis, marked lassitude, and anorexia were the main features of their present illness. The sedimentation rate estimated on admission by the micromethod was above 20 mm. in one hour, and remained elevated for at least six weeks, in the absence of other discoverable causes. At the time the electrocardiogram was recorded, polyarthritis had subsided in most of the children but lassitude, pallor, and anorexia persisted, while the sedimentation rate remained high. This group was further subdivided into two sub-groups, Ia and Ib. The children in sub-group Ia either had at the time of the recording, or developed within a short time after the recording and during the same attack of rheumatic fever, an apical systolic murmur of moderate or loud intensity (Levine's (1933) grade III to grade VI), harsh in

* Since this paper has been submitted for publication, two more articles on this subject have come to our notice. Craige, Alimurung, Blood, and Massull (1950), in an observation of 143 rheumatic children, have presented results which are closely similar to our own, and in a recent paper Taran and Szilagyi (1951) claim further supporting evidence for their earlier work.

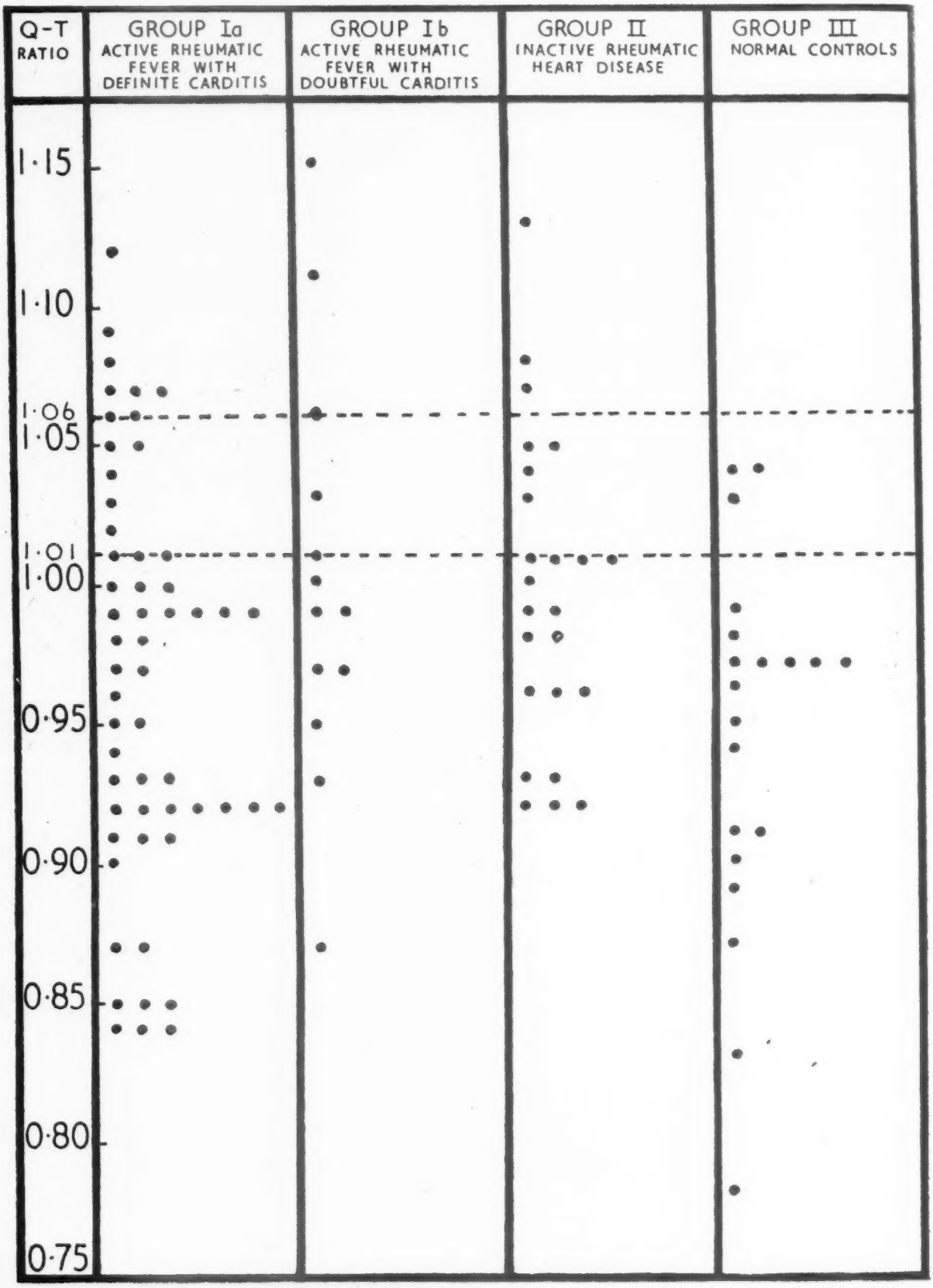


FIG. 1.—Q-T ratios in children with rheumatic infection and in controls.

nature, long, and well conducted to the axilla, or an apical diastolic murmur, or both. These auscultatory findings were always confirmed by more than one observer. In none of these cases was a friction rub heard at any time.

The children in sub-group Ib neither had, nor subsequently developed during the same attack of rheumatic fever, any of the murmurs described above.

**Group II.** This consisted of children who were known to have had an attack of acute rheumatic fever with carditis, as defined by the criteria laid down for sub-group Ia, and in whom one or both of the murmurs described persisted. All clinical signs of activity had, however, subsided at the time of the recording. Only children whose weekly sedimentation rate had been below 10 mm. in one hour for at least two months were included in this group.

**Group III.** The controls were children of the same age group who were admitted for minor surgical operations, and had neither signs of infection nor abnormal cardiac signs.

The number of children and of recordings in each group is shown in Table 1.

TABLE I

NUMBER OF CHILDREN AND RECORDINGS IN THAT GROUP

| Group | Number of Children | E.C.G. Recordings |
|---|---|---|
| Ia. Active rheumatic fever; carditis definite .. | 46 | 55 |
| Ib. Active rheumatic fever; carditis doubtful .. | 12 | 13 |
| II. Inactive rheumatic heart disease .. .. | 24 | 24 |
| III. Normal controls .. | 20 | 20 |
| Total .. .. .. | 102 | 112 |

## Results

**Individual Measurements.** In Fig. 1 the Q-T ratios for the four groups are presented. The lower horizontal line at 1·01 corresponds roughly to a Q-T interval of 0·405 corrected according to Bazett's (1920) formula. It represents the upper limit of normal in Taran's, and Szilagyi's (1947) series. The upper horizontal line at 1·06 corresponds to a corrected Q-T interval of 0·422 which represents the upper limit of normal Q-T interval for children (Ashman and Hull, 1937). This upper limit of normal has been also adopted by Abrahams (1949), while Pokress and Goldberger (1949) place the upper limit of normal even higher, at 1·08.

It can be seen from Fig. 1 that the Q-T intervals of normal children were all below Ashman's and Hull's upper limit of normal, and this maximal normal value can therefore be accepted for the present study. Six recordings in Group Ia, two in Group Ib, and three in Group II showed a Q-T interval above the upper limit of normal.

**Statistical Comparison.** The figures of each group as a whole were compared with those of the other groups, and a difference was accepted as statistically significant when the possibility of its being due to chance was less than 5%. In these children in Group I of whom more than one recording was taken, the mean of the measurements in each child was used in the statistical comparison. There was no statistically significant difference between Group Ia and Group II, namely between children with active and inactive carditis, or between Group I as a whole (Ia and Ib) and Group II. Group I was not significantly different from the control Group III, while there was a significant difference between Groups II and III. Finally all the children with active rheumatic fever or inactive carditis taken together (Group I and II) had a Q-T interval significantly prolonged when compared to the Q-T interval of the 20 controls (Group III).

**Quiescence.** Five of the children in Group Ia eventually became inactive by our criteria. The Q-T intervals of two of these children were longer in the active stage.

## Discussion

The value of the measurement of the Q-T interval in rheumatic fever must be assessed from two different angles. The first, of great practical importance, is whether the measurement helps in the diagnosis of active rheumatic carditis. The second, of more theoretical interest, is whether rheumatic infection exerts any influence at all on the duration of the electrical systole.

In only six of 55 recordings taken during an active rheumatic carditis (sub-group Ia) was the Q-T interval above the maximal normal limit. If to this number are added the children with rheumatic activity, but without definite cardiac involvement, the proportion of lengthened Q-T intervals becomes eight of 68 (11·8%). Three out of 24 children with inactive rheumatic carditis (Group II) had a prolonged Q-T interval (12%). These results suggest that in a case of rheumatic fever a Q-T interval above the normal limit indicates the presence of active rheumatic carditis, but this diagnostic help is available in only a small number of children.

It is evident also that the measurement of the Q-T interval does not help in deciding that rheumatic activity has ceased, since it was prolonged even in cases of inactive rheumatic heart disease.

It may be argued that in the three children in Group II with prolonged Q-T interval there was still latent rheumatic activity. This is unlikely, however, since these three children were allowed gradually to resume their normal life, and there was no evidence of reactivation of the rheumatic fever by the criteria defined.

These results are very different from those of Taran and Szilagyi (1947) and of Abrahams (1949). The former found that 100% of their cases with active rheumatic carditis had a Q-T interval longer than that found in their inactive ones. Unfortunately they do not state in their paper the criteria for the diagnosis of active carditis. In another publication, however, the senior author (Taran, 1947) states that one of the primary clinical criteria of active carditis is 'the disturbance in relationship of systole to diastole.' If such a criterion was indeed used for the selection of cases with active carditis, it is not surprising that all had a lengthened Q-T interval.

Abrahams (1949), on the other hand, defined more clearly the criteria for dividing his cases into active and inactive carditis, and these criteria are similar to those adopted in the present study. It is difficult, therefore, to determine why our findings are so different from his. In Abrahams' (1949) series the Q-T intervals are on the whole longer than our own, and it is unfortunate that in his paper neither the number of normal subjects examined nor the measurements of their Q-T intervals are given. Even from Abrahams' (1949) data it does not appear that the Q-T interval may help in establishing cessation of rheumatic activity, since in five out of 12 cases of inactive carditis the Q-T interval was lengthened. It is true that it was suspected that these five cases were not really inactive, but the reasons for suspecting this inactivity are given for one case only. It seems, therefore, that although rheumatic infection may prolong the duration of electrical systole, the change is so inconstant and slight that it is not often of diagnostic value. Even when it is, it may indicate the presence of rheumatic carditis, but not whether the carditis is active or inactive.

Taran and Szilagyi (1947), and Abrahams (1949) have claimed that repeated measurements of the Q-T interval in the same child indicate a relationship between the duration of the electrical systole and the degree of rheumatic activity. The number of similar cases studied in the present series is too small to justify general conclusions. However, it must be noted that even among the electrocardiograms of five children, two did not demonstrate this relationship.

**Summary**

The Q-T interval was measured in 112 electrocardiograms of 82 children with rheumatic fever and of 20 normal controls.

The Q-T interval was above the maximal normal limit in eight of 68 tracings taken during active rheumatic infection, in three of 24 tracings of children with inactive rheumatic heart disease, and in none of the tracings obtained from the controls.

There was a significant difference between the mean Q-T interval of all the children with active or inactive carditis and the control group.

It is concluded that rheumatic infection may prolong the duration of the electrical systole, but the degree of this change is such that it is of diagnostic value in only a few cases.

We wish to thank Professor E. J. Wayne and Dr. T. Colver for permission to study their cases, Professor R. S. Illingworth for his advice, and Mrs. B. Clapham for statistical help.

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# SERIAL ELECTROCARDIOGRAMS IN RHEUMATIC FEVER

BY

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The management of a patient with acute rheumatic fever depends mainly on the presence or absence of carditis. Numerous tests are available to determine whether or not the heart is affected but none is entirely satisfactory. Taran (1946) found that in 25% of children with active carditis the commonly used tests gave negative results.

As the rheumatic process results in irritation or depression of the myocardium (Pardee, 1947), electrocardiographic abnormalities would be expected to occur often. Since Parkinson, Gosse, and Gunson (1920) described electrocardiographic and polygraphic abnormalities in patients with acute rheumatic fever, almost every part of the electrocardiographic curve has been found to be affected during some phase of the disease. Orgain, Martin, and Anderson (1941) reviewed the abnormalities described, and found their reported incidence to vary from 22% to 100%, depending on the number of records taken in each case. Cohn and Swift (1924) noted frequent prolongation of the A-V conduction time, Blackman and Hamilton (1948) placed most reliance on changes in the ST segment, and Master (1931) commented on the importance of T wave changes. Taran and Szilagyi (1947) and Abrahams (1949) found prolongation of QTc* in 100% and 90% respectively of their cases. Pokress and Goldberger (1949), however, found QTc increased in only 28% of their cases of acute rheumatic fever, and 30% ' never showed K that even reached normal values.' Finally, changes similar to those found in acute rheumatic carditis occur in the electrocardiograms of patients suffering from non-rheumatic infections (Joos and Yu, 1950). It is clear from these investigations that the electrocardiogram in acute rheumatic fever is not diagnostic, and that the changes observed are transient.

If, however, during the course of rheumatic fever a large number of electrocardiograms are obtained, the opportunities for observing these fleeting abnormalities are greatly increased. Serial electrocardiograms help in assessing progress. Minor changes in records taken at frequent intervals become obvious. The changes may only be suggestive of cardiac damage in any one record, but their evolution and regression prove that the rheumatic process is active. The most commonly observed alterations are in the ST segments and the T waves. They can be seen at a glance, and no lengthy calculations are necessary, as for the determination of QTc. Once the disease process has become quiescent, serial tracings will show no further change, as the electrocardiogram in normal persons is strikingly constant over long periods of time (Rothschild, Sacks, and Libman, 1927; Cohn, and Swift, 1924; and others). By means of serial electrocardiograms it is also possible to determine whether a patient who has had a streptococcal infection is likely to develop rheumatic fever, as electrocardiographic evidence often precedes by days or weeks the development of clinical rheumatic fever (Rantz, Boisvert, and Spink, 1945). Finally, it may be worth while pointing out that children much prefer electrocardiographic examinations to the unavoidable needle pricks when estimating the sedimentation rate.

The following seven cases have been selected to show the type of electrocardiographic change that is commonly found. From each patient daily records were obtained for the first week after admission, and thrice weekly thereafter until the patient was either discharged or transferred to a long-stay hospital. All records were taken on a standard string galvanometer with the patient recumbent, and the string tension was standardized to give 10 mm. deflection on 1 m.V. For the determination of K the average length of C and QT was calculated by measuring all complexes in leads I and II. As changes in the precordial leads are also transient and non-specific (Levy and Bruenn, 1934; Ash, 1945), only one example of alterations in a chest lead (CR4) is reproduced. It is recommended that prints be obtained from the films as this simplifies comparison.

* QTc = Bazett's (1920) constant $K = \frac{Q - T}{\sqrt{\text{cycle}}}$

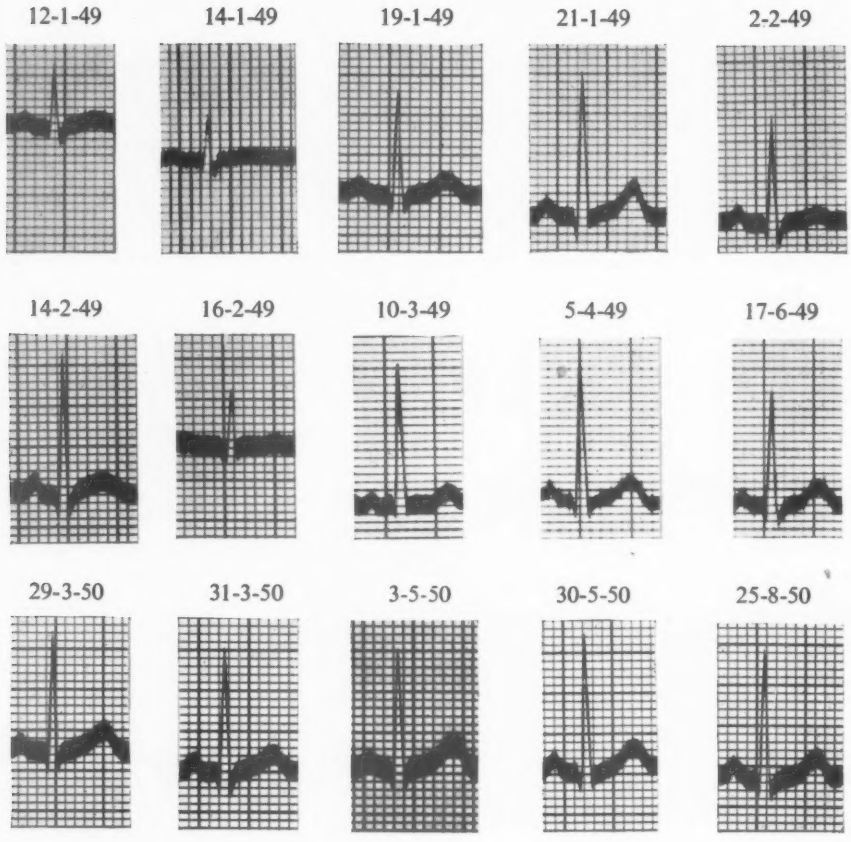


FIG. 1.—All complexes lead II.

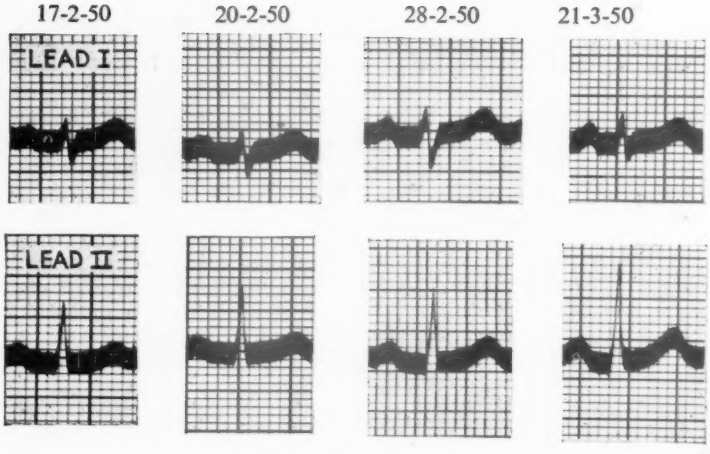


FIG. 2.

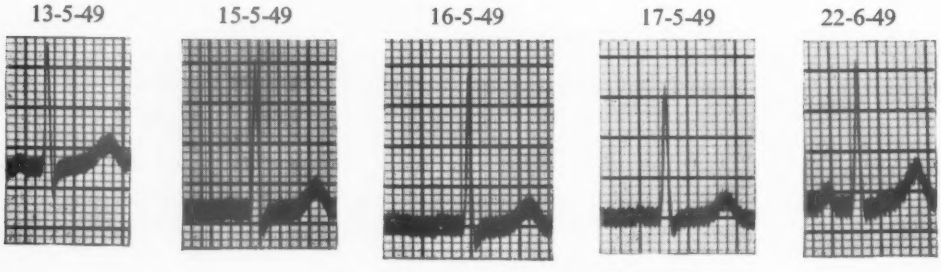


FIG. 3.—All complexes lead II.

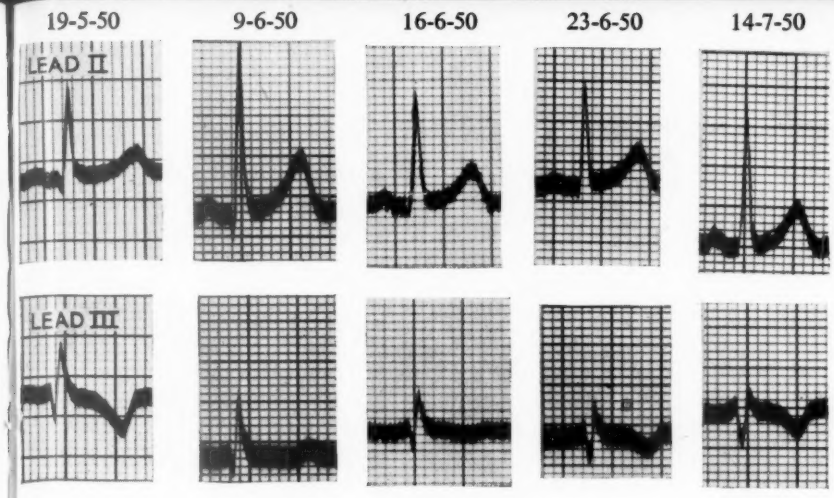


FIG. 4.

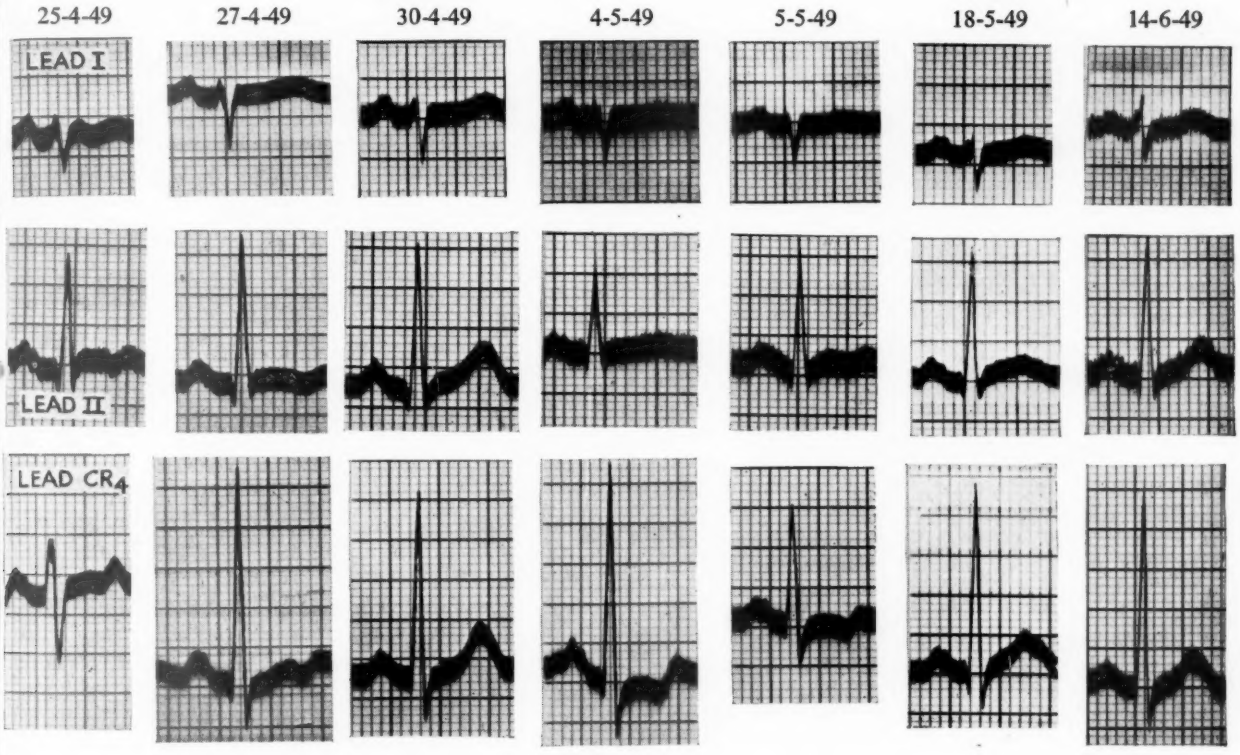


FIG. 5.

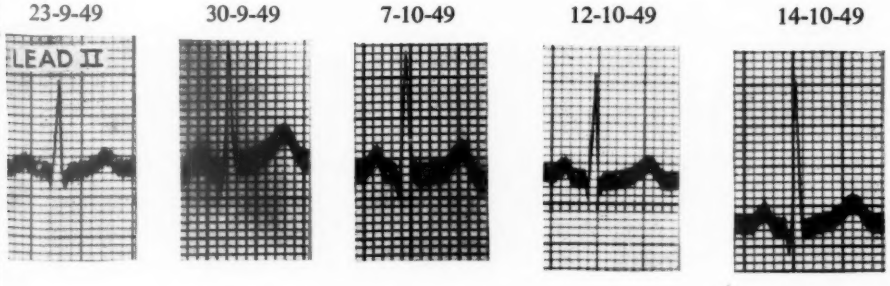


FIG. 6.

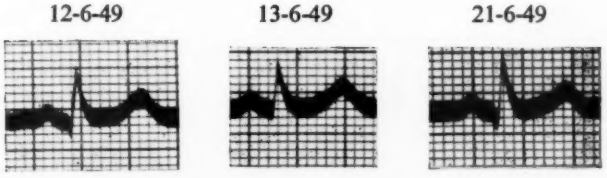


FIG. 7.—All complexes lead I.

### Illustrative Case Summaries

**Case 1.** A boy, aged 10, was admitted on January 11, 1949, with swollen and painful joints, rheumatic carditis, and rheumatic nodules. The temperature was 100° F., sleeping pulse 130, Hb. 60 %, W.B.C. 20,000, E.S.R. 30 mm./hr. A throat swab showed a growth of haemolytic streptococci.

Serial records show waxing and waning of changes in the ST segment and the T wave (Fig. 1).

On June 17 all signs of activity had disappeared, the electrocardiogram was normal, and the child was discharged.

The value for K during the active carditis ranged from 3·19 to 3·92.

The child was readmitted on March 29, 1950, with an attack of anaphylactoid purpura and joint pains. There were no clinical or electrocardiographic signs of carditis, and though the symptoms lasted for two months, the ECG remained unchanged, and has done so since.

**Case 2.** A girl, aged 10, was admitted on February 17, 1950, with joint pains, rheumatic carditis, rheumatic nodules, and erythema marginatum. The ECG showed changes in the amplitude of S in lead I, and of R in lead II (Fig. 2). There were alterations in the contour of ST and in the height of T in lead II. The P-R interval decreased from 0·20 to 0·16. The values for K were 3·82, 4·33, 4·11, 4·45. The carditis was still active at the time of transfer.

**Case 3.** A girl, aged 7, was admitted on May 12, 1950, with flitting joint pains, no abnormal signs in the heart, and slight splenomegaly.

The sedimentation rate was 17 mm./hr, the temperature 98·8° F., and sleeping pulse 90. Symptoms and signs disappeared after ten days, and she has remained well.

The ECG showed disappearance and reappearance of P, and a steady decrease of S (Fig. 3). The record has remained unchanged since June 22, 1950. The values for K were 4·08, 3·54, 3·84, 3·68, 3·80.

**Case 4.** A girl, aged 13, had had scarlet fever for four weeks, and pain in one hip for a week before admission. On admission there were no abnormal signs in joints or heart. The temperature was normal, the sleeping pulse 70, and E.S.R. 6 mm./hr. She was discharged, but readmitted 11 days later with classical rheumatic fever; a systolic murmur at the apex; temperature 99·2° F.; the sleeping pulse 110; E.S.R. 30 mm./hr. The ECG at the time of first admission (May 19) was considered normal, but compared with later tracings showed flat P and raised ST in lead II, and a high R in lead III (Fig. 4). On readmission $T_3$ had become positive and slowly reverted to negative as the disease progressed. The gradual disappearance of $Q_2$, the return of $ST_2$ to isoelectric level, and a decrease in $R_3$ were noted. The values for K were 3·66, 3·82, 3·83, 3·97, 3·80.

**Case 5.** A boy, aged 10, was admitted with rheumatic fever, enlarged heart, systolic and soft diastolic apical murmurs. The temperature was 100·2° F., the sleeping pulse 125, and E.S.R. 53 mm./hr. The child had improved by April 30, 1949, but relapsed on May 4, and then made a steady recovery. There were marked changes in ST and T in all leads (Fig. 5) (There was no clinical evidence of pericarditis.) P-R was prolonged only once (April 25), when it was 0·18 sec. at a rate of 112. At the time of discharge the child was symptom-free and apyrexial (sleeping pulse 70, E.S.R. 10 mm./hr.). The values for K were 4·20, 4·13, 4·28, 4·06, 4·12, 4·08.

**Case 6.** A girl, aged 6, was admitted with pains in the ankles, and systolic and soft diastolic apical murmurs. The temperature was 99° F., the sleeping pulse 90-100, and E.S.R. 15 mm./hr. A throat swab gave a culture of haemolytic streptococci.

She settled down rapidly and was discharged after one month.

The ECG showed progressive raising and lowering of the ST segment, and changes in its contour (Fig. 6). Records taken after October 14, 1949, showed no further change. The values for K were 3·63, 4·10, 4·03, 3·96.

**Case 7.** A boy, aged 7, was admitted with a history of recurrent chorea and a systolic murmur at the apex. The temperature was normal, the sleeping pulse 80, and E.S.R. 4 mm./hr. There were moderate choreic movements.

There was a family history of rheumatic fever. The cardiac signs remained unchanged during his hospital stay, and the chorea had ceased at the time of discharge. The very slight changes in the contour and slope of ST justified the conclusion that the heart had been involved by the rheumatic process (Fig. 7). The values for K were 4·02, 3·86, 3·80, and the curve remained unchanged during the follow-up period.

### Summary

It is the purpose of this paper to emphasize the importance and simplicity of taking serial electrocardiograms for the evaluation of the progress of carditis in acute rheumatic fever. Whilst no individual change in the electrocardiographic curve is necessarily diagnostic, the occurrence of changes from record to record during the course of the disease is of value in deciding how the patient should be managed. Once no further change can be seen in successive tracings, the carditis has ceased. It is suggested that standard limb lead electrocardiograms be obtained daily during the early course of the carditis, and three times a week thereafter.

I wish to express my thanks to Miss Ellis of the Lewisham Hospital for her help in printing the electrocardiograms.

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# ELECTRICAL CONDUCTIVITY AND CHLORIDE CONTENT OF WOMEN'S MILK

## PART 2 : THE EFFECT OF FACTORS RELATING TO LACTATION

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In Part I it was shown that the electrical conductivity of human milk is positively correlated with its chloride content. It was thought desirable to investigate in some detail the effect on both conductivity and chloride content of various factors connected with the time and mode of obtaining milk. Comparisons have been made between (1) fore-milk (milk taken just before a child is fed) and after-milk (milk taken just after a breast feed), (2) milk samples taken in the early morning, at mid-day, and in the evening, (3) milk samples taken at various stages of lactation, i.e., in the first, second, third, fourth, and fifth months of lactation, and (4) milk samples taken from right and left breasts respectively.

### Comparison of Fore-milk and After-milk

From each of 62 women a specimen of milk was taken before and another taken after a breast feed, and the electrical conductivity and chloride content of each of 124 specimens was determined as soon as possible after taking the sample. Of the 62 women, some had an adequate milk supply, but in others there were signs that the lactation was inadequate. Their infants failed to gain weight and received less than 2 oz. of breast milk per lb. body weight each day. The average of the values for electrical conductivity of the 62 specimens of after-milk was $231 \cdot 1 \times 10^{-5} \pm 7 \cdot 38 \times 10^{-5}$ ohm$^{-1}$ cm.$^{-1}$, whilst the corresponding figure for fore-milk was $219 \cdot 4 \times 10^{-5} \pm 8 \cdot 29 \times 10^{-5}$ ohm$^{-1}$ cm.$^{-1}$. The average chloride contents for the two series of milks were $67 \cdot 7 \pm 5 \cdot 12$ mg. and $75 \cdot 2 \pm 6 \cdot 13$ mg. per 100 ml. respectively. It will be seen that the values are lower in the fore-milk than in the after-milk. Using the standard errors, we find that the differences are not significant. This method of comparison, however, does not allow for the fact that the fore-milk and after-milk observations have been made on the same series of women. We have, therefore, taken the differences between the values of the two samples of milk obtained from each woman and applied tests to ascertain whether the mean of these differences differs significantly from zero. The result is that the average of the differences of the conductivity values between fore-milk and after-milk does differ significantly from zero ($t = 3 \cdot 1$), but for the chloride content the result is just significant ($t = 2 \cdot 1$). Hence, it may be concluded that the tendency for after-milk to have higher electrical conductivity and chloride values than fore-milk is a real one. Similar observations were made by Sisson and Denis (1921), Macy, Nims, Brown, and Hunscher (1931) and Ishii (1937), but their results were not statistically analysed. These authors were agreed that the values for after-milk could be either greater or smaller than those for fore-milk. Thus, when making investigations into either the electrical conductivity or chloride content of milk, all milk samples should be taken either before a breast-feed or after a breast-feed, unless the daily milk yield can be obtained for examination.

### Comparison of Morning, Mid-day, and Evening Milk

Samples of milk from two series of women were examined. The first series consisted of 219 women of whom 131 had sufficient milk for their infants and 88 had not. The second series contained 123 women of whom 81 had an adequate, and 42 an inadequate, milk supply. In the first series, two specimens were taken from each woman, both from the same breast, one before a morning feed at 6 a.m., and the second before the noon or 2 p.m. feed. In the second series, three specimens were taken from each woman, all from the same breast, one before the early morning, the second before the mid-day, and the third before the evening feed (the latter at 10 p.m.).

The observations on the electrical conductivity and chloride values of the milks are contained in Tables 1A and 1B. Average values are given for the first month of lactation and for the second to fifth months, the women in each of these groups being divided into two sub-groups, those with adequate and those with inadequate lactation. Both electrical conductivity and chloride values tend to be lowest at early morning, and highest at mid-day.

TABLE 1A

AVERAGE ELECTRICAL CONDUCTIVITY VALUES OF MILK SAMPLES TAKEN IN THE FIRST AND SECOND TO FIFTH MONTHS OF LACTATION

| Type of Lactation | Time of Withdrawing Sample | Average Conductivity $\times 10^5$ ohm$^{-1}$ cm.$^{-1}$ Series I | | Average Conductivity $\times 10^5$ ohm$^{-1}$ cm.$^{-1}$ Series II | |
|---|---|---|---|---|---|
| | | 1st Month | 2nd-5th Month | 1st Month | 2nd-5th Month |
| Adequate | Morning .. | 214·0±4·06 (65)* | 180·8±1·97 (63) | 216·4±5·27 (39) | 181·7±3·58 (42) |
| | Mid-day .. | 214·4±3·96 (65) | 189·2±4·13 (63) | 224·0±5·14 (39) | 182·6±3·35 (42) |
| | Evening .. | | | 231·4±6·90 (39) | 185·1±2·95 (42) |
| Inadequate | Morning .. | 304·4±11·35 (57) | 293·0±21·81 (31) | 263·3±14·22 (15) | 259·7±15·96 (27) |
| | Mid-day .. | 313·2±14·14 (57) | 306·7±22·68 (31) | 303·1±20·41 (15) | 267·8±17·01 (27) |
| | Evening .. | | | 288·5±13·65 (15) | 257·3±16·43 (27) |

* The number of observations from which each mean and standard error of mean have been calculated is indicated by the figure in brackets.

The data have been submitted to statistical examination by the method of the analysis of variance with the following results. Dealing first with electrical conductivity, we find that in the first series of observations, there is a significant variation between the average values for conductivity of milk taken at the three times throughout the day in the case of women with adequate milk supply during the first month of lactation. For the corresponding women with inadequate lactation, the variation throughout the day is not statistically significant. However, in the second series investigated, the variation of the conductivity throughout the day is significant during the first month of lactation for mothers with an inadequate, as well as for those with an adequate, milk supply. During the second to fifth months of lactation, the variation of the electrical conductivity throughout the day is not significant either in the first or second series of observations; this holds both for mothers with an adequate and those with an inadequate milk supply. Similar results are found in respect of chloride content.

The main result which emerges is that during the first month of lactation, the electrical conductivity and chloride value of women's milk tends to be higher at mid-day and to fall again towards evening. This result is more definite in the case of women with an adequate milk supply; for those with an inadequate milk supply, it is confirmed by the second set of observations, but not by the first where the random fluctuations obscure the significance of the observed differences. During the second to fifth months of lactation, there is no significant variation in the average value for early morning, mid-day, and evening milk specimens.

Previous investigators, who have recorded chloride values for milk specimens taken throughout the day, fail to agree on the time of day when the highest values are obtained (Sisson and Denis, 1921; Macy *et al.*, 1931; and Ishii, 1937).

TABLE 1B

AVERAGE CHLORIDE CONTENT OF MILK SAMPLES TAKEN IN THE FIRST AND IN THE SECOND TO FIFTH MONTHS OF LACTATION

| Type of Lactation | Time of Withdrawing Sample | Average Chloride (mg. % calculated as NaCl.) Series I | | Average Chloride (mg. % calculated as NaCl.) Series II | |
|---|---|---|---|---|---|
| | | 1st Month | 2nd-5th Month | 1st Month | 2nd-5th Month |
| Adequate | Morning .. | 65·0±2·39 (66)* | 44·7±1·06 (65) | 76·6±4·79 (39) | 49·9±2·80 (42) |
| | Mid-day .. | 71·0±2·64 (66) | 49·7±2·63 (65) | 78·3±3·42 (39) | 51·8±2·53 (42) |
| | Evening .. | | | 87·0±6·27 (39) | 50·9±2·45 (42) |
| Inadequate | Morning .. | 131·6±8·89 (57) | 126·0±16·13 (31) | 109·3±10·19 (15) | 112·3±12·20 (27) |
| | Mid-day .. | 149·2±9·05 (57) | 134·0±15·49 (31) | 141·4±16·31 (15) | 116·2±13·45 (27) |
| | Evening .. | | | 129·9±11·67 (15) | 109·7±10·67 (27) |

* The number of observations from which each mean and standard error of mean have been calculated is indicated by the figure in brackets

TABLE 2A

AVERAGE ELECTRICAL CONDUCTIVITY OF MILK SAMPLES TAKEN FROM WOMEN WITH ADEQUATE LACTATION

| Time of Withdrawal of Sample | Series | Average Conductivity $\times 10^5$ ohm$^{-1}$ cm.$^{-1}$ | | | Average Conductivity $\times 10^5$ ohm$^{-1}$ cm.$^{-1}$ | | | |
|---|---|---|---|---|---|---|---|---|
| | | 2 weeks | 3 weeks | 4 weeks | 2 months | 3 months | 4 months | 5 months |
| Morning | I | 222 (44)* | 205 (13) | 188 (8) | 183 (28) | 180 (18) | 176 (7) | 179 (10) |
| | II | 222 (32) | 197 (5) | 172 (2) | 193 (8) | 202 (2) | 188 (8) | 174 (24) |
| Mid-day | I | 225 (44) | 207 (13) | 204 (8) | 188 (28) | 194 (18) | 189 (7) | 183 (10) |
| | II | 230 (32) | 206 (5) | 167 (2) | 202 (8) | 201 (2) | 182 (8) | 174 (24) |
| Evening | II | 239 (32) | 206 (5) | 168 (2) | 202 (8) | 197 (2) | 181 (8) | 180 (24) |

* The number of observations from which each mean has been calculated is indicated by the figure in brackets.

**The Effect of the Stage of Lactation**

The women investigated were divided into seven groups depending on the length of time for which they had been lactating; the groups included women who had been lactating two, three, and four weeks, and two, three, four, and five months respectively. The results of the conductivity and chloride content measurements are summarized in Tables 2A, 3A, 2B, and 3B. It will be observed that in Tables 2A, 3A, 2B, and 3B the groups are sub-divided to give values separately for mothers with adequate and inadequate lactation and also for milk samples taken in the morning, at mid-day, and in the evening.

In general, the values for both electrical conductivity and chloride content are higher for samples taken in the second, third, and fourth week of lactation than for those taken in the second, third, fourth and fifth month of lactation. This is brought out in Tables 1A and 1B, which afford a comparison of average values for the first month as a whole with those for the second, third, fourth, and fifth months taken together.

The application of the analysis of variance to these data showed that in the mothers with adequate lactation, the difference between values for the first month and those for the other months was statistically significant, but was insignificant for mothers with inadequate lactation. This is true both in respect of electrical conductivity and chloride content and holds for specimens taken either in the early morning, at mid-day, or in the evening. On the other hand, no significant variation was found, even for mothers with adequate lactation, during the second, third, fourth, and fifth months of lactation either in respect of electrical conductivity or chloride content.

It will be noted that the study differs from that involving the sampling of milk at different times of day, because in the latter each woman gave three specimens which were compared, whereas in the present comparison, the women, say in the fifth month of lactation, were in general, different from those in the second week of lactation. In the statistical analysis, this difference in the structure of the experiments was taken into account. Naturally, when the individuals examined are different in the two groups, the degree of

TABLE 2B

AVERAGE CHLORIDE CONTENT OF MILK SAMPLES TAKEN FROM WOMEN WITH ADEQUATE LACTATION

| Time of Withdrawal of Sample | Series | Average Chloride (mg. % calculated as NaCl.) | | | Average Chloride (mg. % calculated as NaCl.) | | | |
|---|---|---|---|---|---|---|---|---|
| | | 2 Weeks | 3 Weeks | 4 Weeks | 2 Months | 3 Months | 4 Months | 5 Months |
| Morning | I | 68·0 (45)* | 62·0 (13) | 52·0 (8) | 44·0 (29) | 46·0 (18) | 43·0 (7) | 46·0 (11) |
| | II | 81·6 (32) | 57·8 (5) | 45·5 (2) | 48·4 (8) | 65·0 (2) | 55·5 (8) | 47·5 (24) |
| Mid-day | I | 76·0 (45) | 64·0 (13) | 67·0 (8) | 46·0 (29) | 56·0 (18) | 50·0 (7) | 49·0 (11) |
| | II | 83·7 (32) | 57·8 (5) | 43·0 (2) | 56·2 (8) | 67·5 (2) | 55·4 (8) | 47·8 (24) |
| Evening | II | 93·3 (32) | 61·4 (5) | 50·0 (2) | 52·6 (8) | 60·0 (2) | 50·2 (8) | 48·0 (24) |

* The number of observations from which each mean has been calculated is indicated by the figure in brackets.

TABLE 3A

AVERAGE ELECTRICAL CONDUCTIVITY OF MILK SAMPLES TAKEN FROM WOMEN WITH INADEQUATE LACTATION

| Time of Withdrawal of Samples | Series | Average Conductivity $\times 10^5$ ohm$^{-1}$ cm.$^{-1}$ | | | Average Conductivity $\times 10^5$ ohm$^{-1}$ cm.$^{-1}$ | | | |
|---|---|---|---|---|---|---|---|---|
| | | 2 Weeks | 3 Weeks | 4 Weeks | 2 Months | 3 Months | 4 Months | 5 Months |
| Morning | I | 311 (38)* | 294 (15) | 278 (4) | 337 (15) | 259 (6) | 258 (8) | 202 (2) |
| | II | 301 (2) | 252 (5) | 261 (8) | 268 (13) | 258 (9) | 216 (2) | 260 (3) |
| Mid-day | I | 314 (38) | 312 (15) | 314 (4) | 361 (15) | 264 (6) | 261 (8) | 210 (2) |
| | II | 278 (2) | 297 (5) | 314 (8) | 285 (13) | 244 (9) | 281 (2) | 259 (3) |
| Evening | II | 288 (2) | 275 (5) | 297 (8) | 270 (13) | 239 (9) | 237 (2) | 274 (3) |

* The number of observations from which each mean has been calculated is indicated by the figures in brackets.

variation to be expected is greater and so any real difference has less chance of showing itself. It is, therefore, advantageous to have the individuals in the two groups either the same or paired to resemble each other closely. This, however, was not practicable. It is possible that, had the numbers been larger, the electrical conductivity and chloride content of milk at the later stages of lactation might have proved to be significantly lower than the values at the earlier stage for women with inadequate as well as for those with adequate lactation.

The fall in chloride content of women's milk after the first month of lactation is in agreement with the findings of Holt, Courtney, and Fales (1915). Other observers however (Sisson and Denis, 1922; Widdows, Lowenfeld, Bond, Shiskin, and Taylor , 1935; and Ishii, 1937) did not observe any appreciable change in the chloride content of milk taken from women in the second week to fifth months of lactation.

**Comparison of Samples from Right and Left Breasts**

Determinations have been made of the electrical conductivity and chloride content of samples of the fore-milk taken from each of the right and left breasts of 152 women. The specimens were taken from women at different stages of lactation and from women with adequate and inadequate supply, but it is impractical to differentiate between the various types. Both electrical conductivity and chloride content values of the two samples taken from the same women often showed considerable differences. Thus the mean of the absolute value of the differences of the electrical conductivities was $30{\cdot}2 \times 10^{-5}$ ohm$^{-1}$ cm.$^{-1}$, whilst that of the chloride content was 23·5 mg. per 100 ml. However, although in any one woman there might be a considerable difference between the values for the two breasts, there was no general tendency for the right breast to give either higher or lower values than the left breast. Thus the average electrical conductivity was $208{\cdot}7 \times 10^{-5}$ ohm$^{-1}$ cm.$^{-1}$ for the samples from the right breast and $205{\cdot}7 \times 10^{-5}$ ohm$^{-1}$ cm.$^{-1}$ for those from the left breast. The corresponding figures for the chloride contents were 64·3 mg. % and 64·4 mg. %. These differences of means are not statistically

TABLE 3B

AVERAGE CHLORIDE CONTENT OF MILK SAMPLES TAKEN FROM WOMEN WITH INADEQUATE LACTATION

| Time of Withdrawal of Samples | Series | Average Chloride (mg. % calculated as NaCl.) | | | Average Chloride (mg. % calculated as NaCl.) | | | |
|---|---|---|---|---|---|---|---|---|
| | | 2 Weeks | 3 Weeks | 4 Weeks | 2 Months | 3 Months | 4 Months | 5 Months |
| Morning | I | 137·0 (38)* | 120·0 (15) | 125·0 (4) | 157·0 (15) | 100·0 (6) | 102·0 (8) | 70·0 (2) |
| | II | 118·5 (2) | 93·8 (5) | 116·6 (8) | 122·5 (13) | 104·1 (9) | 75·5 (2) | 116·5 (3) |
| Mid-day | I | 140·0 (38) | 133·0 (15) | 145·0 (4) | 175·0 (15) | 104·0 (6) | 96·0 (8) | 73·0 (2) |
| | II | 116·0 (2) | 132·0 (5) | 153·6 (8) | 134·8 (13) | 136·2 (9) | 124·0 (2) | 119·7 (3) |
| Evening | II | 116·0 (2) | 121·8 (5) | 138·4 (8) | 122·0 (13) | 89·1 (9) | 89·5 (2) | 131·3 (3) |

* The number of observations from which each mean has been calculated is indicated by the figure in brackets.

significant, nor is the mean of the differences between the values for right and left breasts significantly different from zero, for either the electrical conductivity or the chloride content.

These results are in conformity with those reported by Nozaki (1934) and Ishii (1937 and 1938) who found that, on the average, the chloride content of milk from the right breast was almost the same as that for milk from the left breast, but that the chloride content of the milk from the two breasts of any one woman may differ considerably. It is obvious, in view of these findings, that in using either the electrical conductivity or the chloride content of the milk to assess the probable value of a mother's milk, it is important to make observations on samples from both the right and left breasts.

## Discussion

The work reported here reveals the importance of sampling milk for examination with sufficient care if the specimens are to be used to help in assessing the quality of the milk and the probable adequacy of the lactation. It has been shown that in mothers with adequate lactation, the electrical conductivity and chloride content of the milk tend to fall during the second to fourth week, after which they remain approximately constant. In the same mother, there appears to be a rise between early morning and mid-day and the milk from the two breasts may differ very considerably, although there is no general tendency for the milk from the right breast to give either higher or lower values than that from the left. In view of these variations, it is suggested that samples should be taken at least twice a day (before the morning and before the mid-day feed) and that, on each occasion, one sample should be taken from each breast. In assessing the quality of the milk, the values obtained should be compared with standards varying according to the period of lactation. It is suggested that from women with adequate lactation milk should give values which do not significantly exceed the average values shown in Tables 1A and 1B. Milk which gives values for electrical conductivity and chloride content substantially above these averages is to be regarded with suspicion.

## Summary

A study has been made of the effect of various factors on the electrical conductivity and chloride content of women's milk. In general, the electrical conductivity and chloride content run closely parallel.

The electrical conductivity and chloride content of milk is generally somewhat greater in samples taken after a breast feed than in samples taken before a breast feed.

Samples of milk taken before the mid-day feed tend to have a higher electrical conductivity and chloride content than samples taken before the morning or evening feeds, but this difference is significant only in the first month of lactation.

The electrical conductivity and chloride content of samples of milk taken from women with adequate milk supply at various periods of lactation show a tendency to fall from the second to the fourth weeks, which is statistically significant, but from this point onwards there is, on the average, no significant variation. In women with inadequate lactation, who show greater variation in the electrical conductivity and chloride content, the variations at the different periods of lactation were not statistically significant.

On the average, milk samples taken from the right breasts of women do not differ significantly from samples taken from the left breasts, but in any one woman the difference in electrical conductivity and chloride content may be considerable. Samples of milk taken from only one breast may give misleading results.

The bearing of these findings on the procedure to be adopted in sampling milk in order to determine the adequacy of lactation is discussed.

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# PART 3 : RELATIONSHIP TO ADEQUACY OF LACTATION

BY

R. A. MILLER

For at least 50 years observations have been made on the chloride content of women's milk. Some of the results suggest a relationship between the chloride content of the milk and either the adequacy of lactation or the milk yield, the chloride values below 50 mg. % being usually associated with adequate and those above 50 mg. % with inadequate lactation (Holt, Courtney, and Fales, 1915; Sisson and Denis, 1921; Widdows, Lowenfeld, Bond, Shiskin, and Taylor, 1935; Nozaki, 1934; Ishii, 1937). It has been shown in Part II that there is not only a relationship between the chloride content of milk and adequacy of lactation, but also a relationship between the electrical conductivity of milk and adequacy of lactation, the average values for both being lower in women with adequate than in those with inadequate lactation. However, a proportion of the women with poor lactation had milk of low chloride content and low conductivity while some women with adequate lactation had milk of relatively high chloride content and conductivity.

To decide whether the determination of either the chloride content or the electrical conductivity of women's milk was of practical value, a series of 538 specimens of milk from women in the second week to the fifth month of lactation inclusive were examined; 352 were taken from women with adequate lactation, and 186 from women with inadequate lactation. The mothers providing the samples of milk gave two specimens from the same breast, one before the 6 a.m. feed and the other before the mid-day feed (12 p.m. or 2 p.m.) on the same day.

A second series of observations involving the chloride estimation and the electrical conductivity measurement of milk taken from both breasts of each woman was considered necessary, in view of a number of anomalous results obtained in the first series. One hundred and thirty-six specimens of milk taken during the third week to fifth month of lactation were examined; 72 were obtained from mothers with adequate lactation, and 64 from mothers with inadequate lactation. The mothers providing samples gave one from each breast before the 6 a.m. feed and one from each breast before the mid-day breast feed. All specimens obtained from each mother were collected in separate containers and tested separately. In both series of cases, each sample amounted to about 8 ml. and was expressed into a special container that had been thoroughly cleansed, rinsed in distilled water, and dried in an oven.

All the mothers were apparently healthy and had given birth to a mature infant which fixed well at the breast and was fed at regular intervals five or six times a day. The infants were apparently normal at the time of the test. The choice of a mother with adequate lactation was made by noting that her infant was gaining weight while it was entirely breast fed. Women with inadequate lactation were selected by first finding a mother whose infant was healthy, but who was not gaining weight, or who required complementary feeds. Such infants were then test-fed for at least 24 hours. If the results showed that the babies did not receive 2 oz. milk per lb. body weight per day, they were considered to be under-fed.

The methods of estimation have been described in Part 1.

### Results of Chloride Investigation

A summary of the results of both series of investigations on the chloride content is given in Fig. 1, which shows the mean chloride content of the early morning and mid-day milk specimens obtained from a given breast. The values obtained from mothers with inadequate lactation are generally higher than those from mothers with adequate lactation. In Fig. 1 the results are divided according to the time after parturition at which the milk sample was taken. For each of these weekly or monthly stages, a level has been chosen above which lies the majority of chloride values for milk obtained from women with inadequate lactation and below which lies the majority of values for women with adequate lactation. This ' critical ' level for milk specimens taken in the third and fourth weeks of lactation is 75 mg. NaCl. per 100 ml. milk; for milk taken in the second month it is at 60 mg. NaCl., and for milk taken in the third to fifth months it is at 55 mg. NaCl. For milk taken during the second week of lactation, the division is not so clear-cut, and therefore, two ' critical ' levels instead of one are necessary, the lower being at 75 mg. NaCl. per 100 ml. milk, and the higher at 112 mg. NaCl. per 100 ml. milk. Values below the lower critical level are usually associated with adequate lactation, while

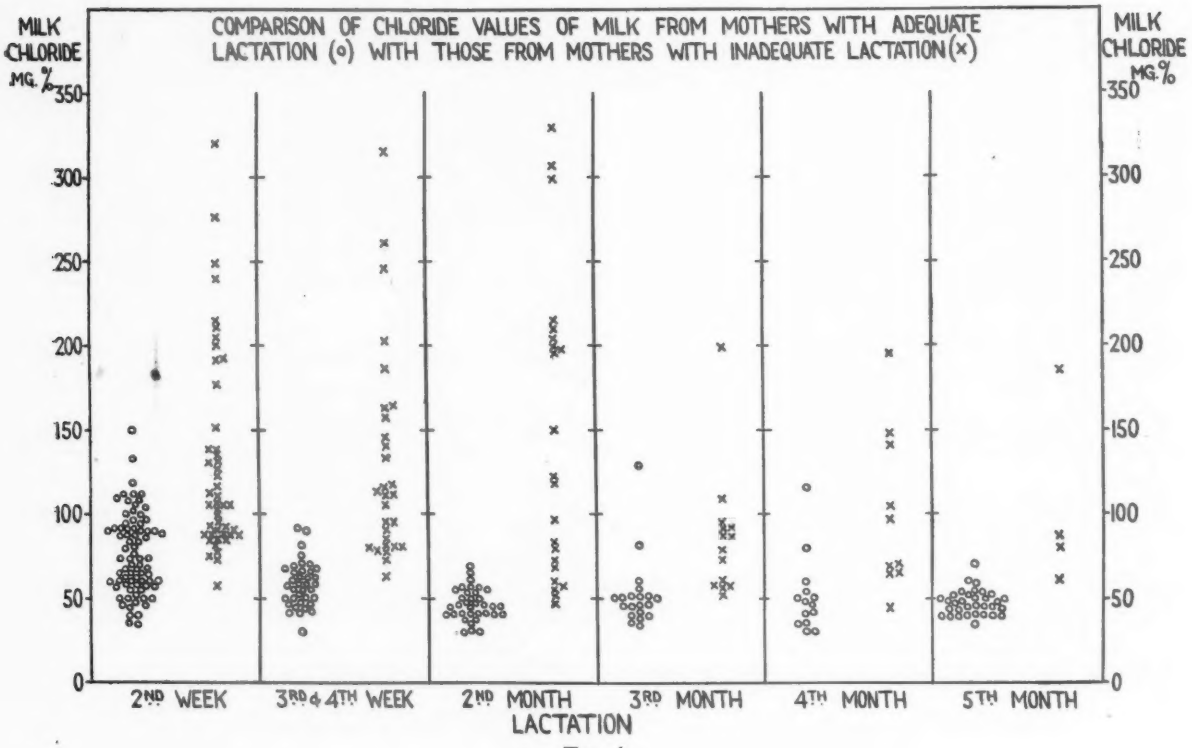


FIG. 1.

those above the upper critical level are generally associated with inadequate lactation. Values lying between the two critical levels are without diagnostic significance.

If the mother's milk chloride lies below the critical level, it is likely that she can satisfy her infant on the breast. If it falls above, she is probably not producing enough milk to meet her infant's requirements. For 11·9% of the mothers with an adequate supply (series I) in the third week to fifth month of lactation the chloride test was misleading because the chloride values were above the critical level, which suggested that these women had inadequate lactation. Similarly, anomalous results were obtained for 17·4% of the mothers (series I) with an inadequate supply in the third week to fifth month of lactation whose milk had a chloride content below the critical level.

Some light has been shed on the origin of the majority of these anomalous results (series I) by the results obtained for the chloride content of milk taken from both breasts of women in the third week to fifth month of lactation (series II). In this series, 22 women were lactating adequately and 22 inadequately. It was noted that three of the women with adequate lactation and five of those with inadequate lactation had one breast functioning well and the other functioning badly, as judged by the comparison of milk chloride from each breast with the relevant critical chloride level. In such cases, therefore, the chloride test did not reveal whether or not these women were lactating adequately, and it was necessary to depend on the results of test-feeding of the infants to decide whether the mother's lactation was adequate.

The extent to which unilateral breast dysfunction accounts for anomalous results in the milk chloride test depends on its frequency. Judging from the series of 44 cases, it was present in three out of 22, or 13·6% of mothers with adequate lactation, and in five out of 22, or 22·7% of mothers with inadequate lactation. It is to be expected that the accuracy of the test could be considerably increased by testing both breasts.

When considering anomalous results obtained in the first series, another explanation must be kept in mind. In two mothers in the second series of 44 cases, the milk from both breasts had a chloride content below the critical level and yet the milk output was inadequate. This type of breast function may be due to hypoplasia of the gland tissue. Breast disorders of this nature cannot be detected by the milk chloride test and will, consequently, remain a source of error.

In conclusion, it can be said that the milk chloride test is a valuable indication as to whether or not a

mother is lactating adequately, particularly if both breasts are tested and the results are in agreement. If the chloride content of milk from one breast is below the critical level, while that of milk from the other breast is above the critical level, no definite decision as to the adequacy of lactation can be made and in such a case it is desirable that the mothers' infants should be test-weighed.

It seems clear that in a few cases mothers may have a low chloride value for milk from both breasts and yet have an inadequate milk yield. The type of case, however, appeared to be of infrequent occurrence, only two being encountered in 44 cases. The fact that they do exist reduces the value of this test as a method of assessing adequacy of lactation.

**Results of Electrical Conductivity Measurements**

A summary of the electrical conductivity measurements of both series of cases is presented (Fig. 2) in a similar way to those of the milk chloride investigation. Fig. 2 shows that the conductivity values of milk taken from mothers with inadequate lactation are generally higher than those for milk taken from mothers with adequate lactation. As in the case of chloride values, it is possible to fix a 'critical' level for each stage of lactation below which lies the majority of values for women with adequate lactation, and above which lies the majority of values for women with inadequate lactation. The critical level of milk specimens taken during the third and fourth week of lactation is at $225 \times 10^{-5}$ ohm$^{-1}$ cm.$^{-1}$; for milk taken in the second month of lactation it is at $210 \times 10^{-5}$ ohm$^{-1}$ cm.$^{-1}$; and for milk taken in the third to fifth month of lactation it is at $200 \times 10^{-5}$ ohm$^{-1}$ cm.$^{-1}$. For milk taken in the second week, two critical levels are used for diagnostic purposes, the lower one at $225 \times 10^{-5}$ ohm$^{-1}$ cm.$^{-1}$ and the higher one at $275 \times 10^{-5}$ ohm$^{-1}$ cm.$^{-1}$. Values below the lower critical level are generally associated with adequate lactation, while those above the upper critical level are usually associated with inadequate lactation. Values lying between the two critical levels are without diagnostic significance.

The importance of the critical levels in distinguishing cases of good lactation from those of bad lactation is shown by the fact that 92·1% of the women (series I) with an adequate supply in the third week to fifth month of lactation had values

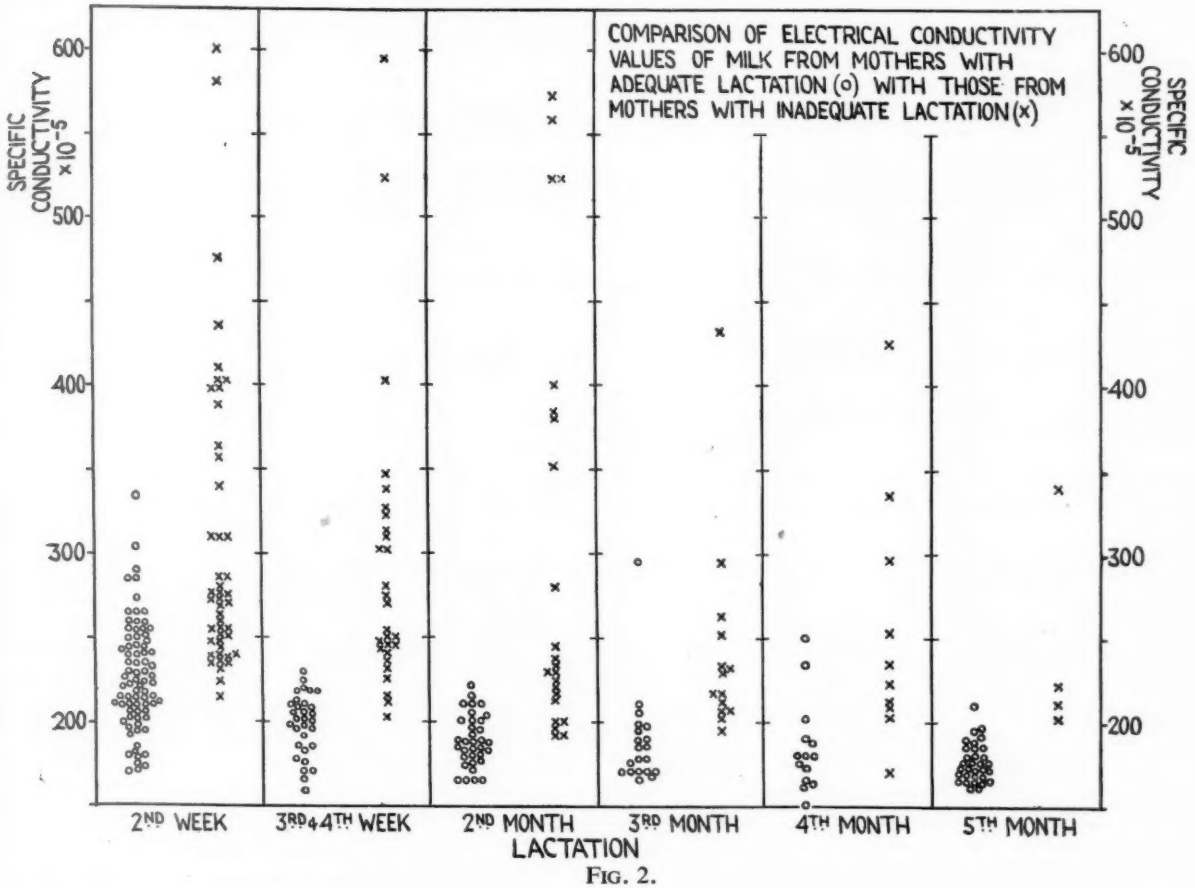


FIG. 2.

below the relevant critical level, and 89·9% of the women (series I) with an inadequate supply in the third week to fifth month had values above the critical level.

The results of the electrical conductivity estimations made on milk obtained from a series of 44 women who had both breasts tested during their third week to fifth month of lactation have elucidated some of the anomalous conductivity results obtained in the first series. Thus, in the series of 44 women, three women with adequate lactation and five with inadequate lactation have unilateral breast dysfunction as judged by the electrical conductivity test. These findings are similar to those obtained in the second series of observations on the milk chloride test.

The incidence of unilateral breast dysfunction in the series of 44 cases is three to 22, or 13·6% of mothers with adequate lactation, and is five to 22, or 22·7% of mothers with inadequate lactation. The percentage is considerable, and it is probable that many of the anomalous cases noted in the first series had unilateral breast dysfunction. In order to detect such cases, and thus to increase the accuracy of the electrical conductivity test, milk from both breasts must be tested. In cases of unilateral breast dysfunction adequacy of lactation cannot be assessed by the conductivity test alone.

There was one other anomalous result in the second series, apart from those due to unilateral breast dysfunction. In this case, the conductivity value of milk from both breasts was below the relevant critical level, and yet the mother was lactating inadequately. A similar result was obtained from the chloride values of the same woman. The explanation is obscure, but the phenomenon is possibly due to hypofunction of the breast, resulting from lack of secretory tissue.

The conclusions drawn from the investigation on the electrical conductivity of milk are similar to those for the investigation on the chloride content of milk. The electrical conductivity test is a valuable indication of the adequacy of lactation, particularly if both breasts are tested and the results from both are similar. If the conductivity value of milk from one breast is below the relevant critical level, but that of the other is above the critical level, no definite decision on the adequacy of lactation can be made. In such cases, the infants should be test-weighed.

## Discussion

In the past it has been shown that women between the second week and the fifth month of lactation and with a milk chloride content of less than 50 mg. % usually lactated adequately but those with a milk chloride of more than 50 mg. % usually lactated inadequately (Sisson and Denis, 1921; Nozaki, 1934; Widdows *et al.*, 1935; Ishii, 1937). The chloride level of 50 mg. % quoted by previous investigators is analogous to the five critical levels selected in the present investigation.

The factors which may be responsible for the marked variation in the chloride content of milk being detected only in the present series of women are numerous. The nationality, climatic conditions, and diet of the women differed from those investigated in the past. It is probable that the salt intake for each series of women under investigation was not constant, and if the intake had been increased (Baldassi, 1941) or diminished sufficiently (Sacco, 1932, quoted by Dickinson, 1935) the chloride content of their milk might have altered. Differing methods of milk sampling may also account for the lack of uniformity in the results obtained by different investigators.

## Summary

Estimations of the chloride content and electrical conductivity have been made on specimens of milk taken from 420 women with adequate lactation, and 250 women with inadequate lactation, and the results obtained from the two groups compared. The women examined had been lactating for periods ranging from two weeks to five months.

The conclusions drawn from the comparison of the results obtained from the two groups of chloride examinations were the same as those obtained from a comparison of the electrical conductivity values. The two methods of estimation used were equally efficient and both were quick and simple to perform.

It has been shown that the majority of adequately lactating women have milk with a lower chloride content and conductivity value than women lactating inadequately. Thus it has been possible to select both chloride and electrical conductivity values above which most values were for women with inadequate lactation and below which they were usually for women with adequate lactation.

Either the chloride or the electrical conductivity values for women's milk gave a good indication as to the adequacy of lactation, particularly if the milk from both breasts was tested.

Anomalous results limit the practical value of both the chloride and conductivity estimations as a test for adequacy of lactation; in a small proportion of cases a low chloride or conductivity result was obtained in the presence of inadequate lactation and in 18% of a small series of chloride and conductivity estimations made on milk from both breasts separately a high milk yield from one breast and a low yield from the other was demonstrated.

Explanations have been offered for anomalous results. The clinical significance of the anomalous

result which indicated that there was a high milk yield from one breast and a low yield from the other was doubtful, and in such cases further investigation is necessary before deciding the best method of feeding the infant.

The influence of the stage of lactation upon the chloride content of women's milk is discussed.


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# PART 4 : RESULTS AND THEIR RELATIONSHIP TO MILK YIELD AND TO DURATION OF LACTATION


BY

R. A. MILLER and I. I. A. JACKSON


It has been shown that the estimation of electrical conductivity and chloride content of women's milk are of equal value as methods of determining the adequacy of lactation. It is evident that these tests would prove of practical value if it were shown that the electrical conductivity or chloride content of milk from one breast could be correlated with the daily milk yield from that breast, and similarly if these tests when performed on milk taken from women in the first month of lactation were shown to give some indication of the length of time these women would breast-feed their infants. This paper deals with the investigation of these two problems.

## Daily Milk Yield from One Breast Correlated with Electrical Conductivity and Chloride Content

For the correlation of the daily yield from one breast with the electrical conductivity and chloride content of the milk a series of observations was made on women who were breast-feeding their infants. The mothers who were subjected to the investigation were apparently healthy and had infants who fixed well on the breast. Each had been lactating from between two weeks to five months. Forty-nine mothers in the first month of lactation and 61 mothers in the second to fifth month of lactation were tested. The amount of milk secreted by one breast in a day was measured by weighing the infant before and after it was put to that breast. The residual milk was not expressed and measured because this could not be supervised or performed skilfully by every woman who was examined. Every specimen used for conductivity and chloride tests consisted of approximately 4 ml. of milk. One specimen was taken before the early morning feed, one before the mid-day feed, and one before the evening feed, and each was taken on the day that the baby was test-weighed.

### Results

The average daily milk yield for one breast for women secreting milk of a particular electrical conductivity is shown in Table 1A.

The minimum yield was 0·5 oz. when the conductivity of the milk was 371 to $390 \times 10^{-5}$ ohm$^{-1}$ cm.$^{-1}$, the maximum yield was 13·1 oz. with a conductivity of 170 to $190 \times 10^{-5}$ ohm$^{-1}$ cm.$^{-1}$. From Table 1A it is apparent that there is an inverse

TABLE 1A

RELATIONSHIP OF THE MEAN ELECTRICAL CONDUCTIVITY VALUE OF MILK FROM ONE BREAST TO THE DAILY YIELD FROM THE SAME BREAST

| Group | Milk Conductivity ($\times 10^{-5}$ ohm$^{-1}$ cm.$^{-1}$) | Average Milk Volume (oz. per day) | Number of Observations |
|---|---|---|---|
| 1 | 170–190 | 13·1 | 22 |
| 2 | 191–210 | 10·0 | 19 |
| 3 | 211–230 | 7·8 | 25 |
| 4 | 231–250 | 6·3 | 13 |
| 5 | 251–270 | 6·75 | 7 |
| 6 | 271–290 | 5·4 | 6 |
| 7 | 291–310 | 4·3 | 5 |
| 8 | 311–330 | 1·75 | 4 |
| 9 | 331–350 | 2·25 | 3 |
| 10 | 351–370 | 0·5 | 2 |
| 11 | 371–390 | 0·5 | 1 |

relationship between the average milk yield and the electrical conductivity of the milk. It has, however, been shown that the milk volume of individual feeds does not bear a significant relationship to the electrical conductivity of the milk taken at the beginning of that feed (Miller, 1949). The milk yields of individual women who constitute any one group may differ markedly from each other. This variation in milk yield for women secreting milk of a given electrical conductivity value is well shown in Fig. 1a. In this figure the volume of milk obtained from one breast in one day has been plotted against the mean electrical conductivity value of that milk. The daily milk volumes range from 0·4 to 20 oz. per day and the mean conductivity values of milk from 164 to $540 \times 10^{-5}$ ohm$^{-1}$ cm.$^{-1}$. The variation in milk yield between women secreting milk of a given conductivity value differs in extent; this variation is negligible when the conductivity value is in the region of $540 \times 10^{-5}$ ohm$^{-1}$ cm.$^{-1}$, but becomes progressively greater as the conductivity value diminishes, the maximum variation amounting to 20 oz. when women secrete milk with a conductivity of $171 \times 10^{-5}$ ohm$^{-1}$ cm.$^{-1}$. Therefore, this method of investigation does not form a reliable method of determining the milk yield of individual women.

The comparison of milk volume with the chloride content of that milk has been made. The average daily milk yields for women secreting milk with particular percentages of chloride are given in Table 1B, the minimum yield being 1·3 oz. per day when the milk contains 181 to 200 mg. chloride and the maximum yield being 10·8 oz. when the milk contains 40 to 60 mg. chloride %. The variation in milk yield for women secreting milk of a given chloride content is shown in Fig. 1b, where the daily volume of milk from one breast has been plotted against the mean chloride value of the milk from the same breast. The milk volumes range from 0·5 to 24 oz. per day and the mean chloride values of milk from 40 to 199 mg. %. The conclusion drawn from the results as presented in Table 1B is that there is an inverse relationship between average milk yield and the chloride content of milk. That obtained from Fig. 1b is that milk yield from women secreting milk of a particular chloride content can vary considerably.

TABLE 1B
RELATIONSHIP OF THE MEAN CHLORIDE VALUE OF MILK FROM ONE BREAST TO THE DAILY YIELD FROM THE SAME BREAST

| Group | Milk Chloride (mg. %) | Average Milk Volume (oz. per day) | Number of Observations |
|---|---|---|---|
| 1 | 40–60 | 10·9 | 44 |
| 2 | 61–80 | 8·35 | 20 |
| 3 | 81–100 | 7·15 | 10 |
| 4 | 101–120 | 6·3 | 14 |
| 5 | 121–140 | 5·2 | 6 |
| 6 | 141–160 | 4·8 | 3 |
| 7 | 161–180 | 2·2 | 3 |
| 8 | 181–200 | 1·3 | 3 |
| 9 | 201–220 | 0·25 | 1 |
| 10 | 221–240 | 0·0 | 1 |

## Discussion

Important deductions can be made, however, from this investigation; when the electrical conductivity of milk is at least $280 \times 10^{-5}$ ohm$^{-1}$ cm.$^{-1}$ or the chloride content of milk is 110 mg. % or more, it is almost certain that the daily milk yield from the breast will not exceed 6 oz. If both breasts have the same functional capacity, the quantity will be inadequate for a normal infant. Secondly, if the electrical conductivity of milk is 260 to $220 \times 10^{-5}$ ohm$^{-1}$ cm.$^{-1}$ or the chloride content of milk is 90 to 70 mg. % during the neonatal period, the daily milk yield from one breast is likely to be 6·3 to 8·35 oz.; therefore, from two breasts it may be 12·5 to 17 oz., and this quantity is usually sufficient for infants 2 to 3 weeks old. Thirdly, mothers in the second to fifth month of lactation must have milk with an electrical conductivity not greater than $200 \times 10^{-5}$ ohm$^{-1}$ cm.$^{-1}$ or 60 mg. % of chloride if their infants are to obtain the amount necessary to maintain their health and normal development.

The estimation of either electrical conductivity or chloride content is valuable if the result is relatively high, i.e. an electrical conductivity over $210 \times 10^{-5}$ ohm$^{-1}$ cm.$^{-1}$ or chloride value over 60 mg. %, but when the electrical conductivity values are less than $210 \times 10^{-5}$ ohm$^{-1}$ cm.$^{-1}$ or chloride values less than 60 mg. %, their significance is sometimes doubtful because the variation in milk yield which accompanies such values is very great and amounts to 20 oz. There are at least two reasons for this great variation in milk yield. The first and most probable explanation is that in almost a third of the cases with relatively low conductivity and chloride values the demand made upon the breast was not great, because the infants suckled were under a month old (values 0 in Figs. 1a and 1b). In such cases, the relatively low quantity of milk obtained almost certainly reflected the demands of the infant rather than the potentialities of the breast. Low milk yields accompanying milk with low conductivity and chloride values may also be due to hypoplasia or to a hypogalactic type of breast. In the present series of observations this condition was diagnosed

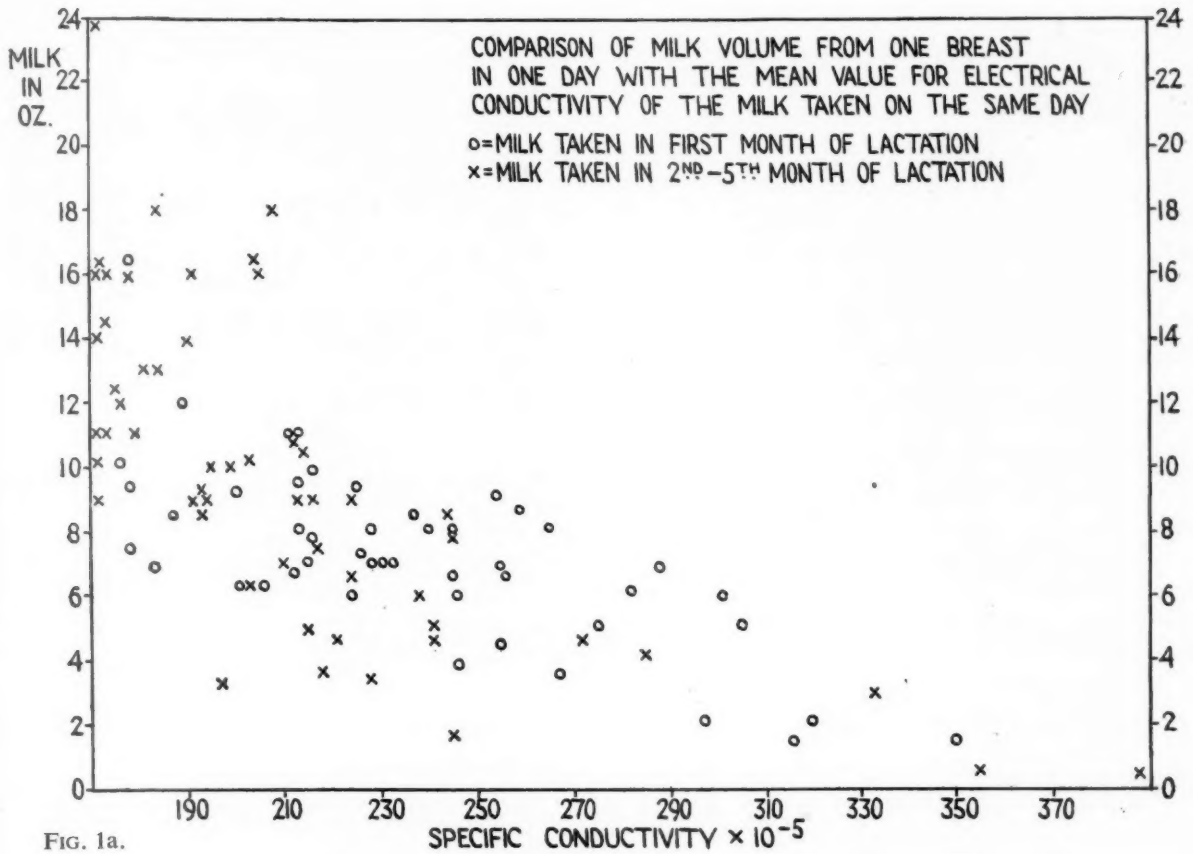
COMPARISON OF MILK VOLUME FROM ONE BREAST
IN ONE DAY WITH THE MEAN VALUE FOR ELECTRICAL
CONDUCTIVITY OF THE MILK TAKEN ON THE SAME DAY
o=MILK TAKEN IN FIRST MONTH OF LACTATION
x=MILK TAKEN IN 2ND–5TH MONTH OF LACTATION
MILK IN OZ.
SPECIFIC CONDUCTIVITY × 10⁻⁵
0
2
4
6
8
10
12
14
16
18
20
22
24
190
210
230
250
270
290
310
330
350
370

FIG. 1a.

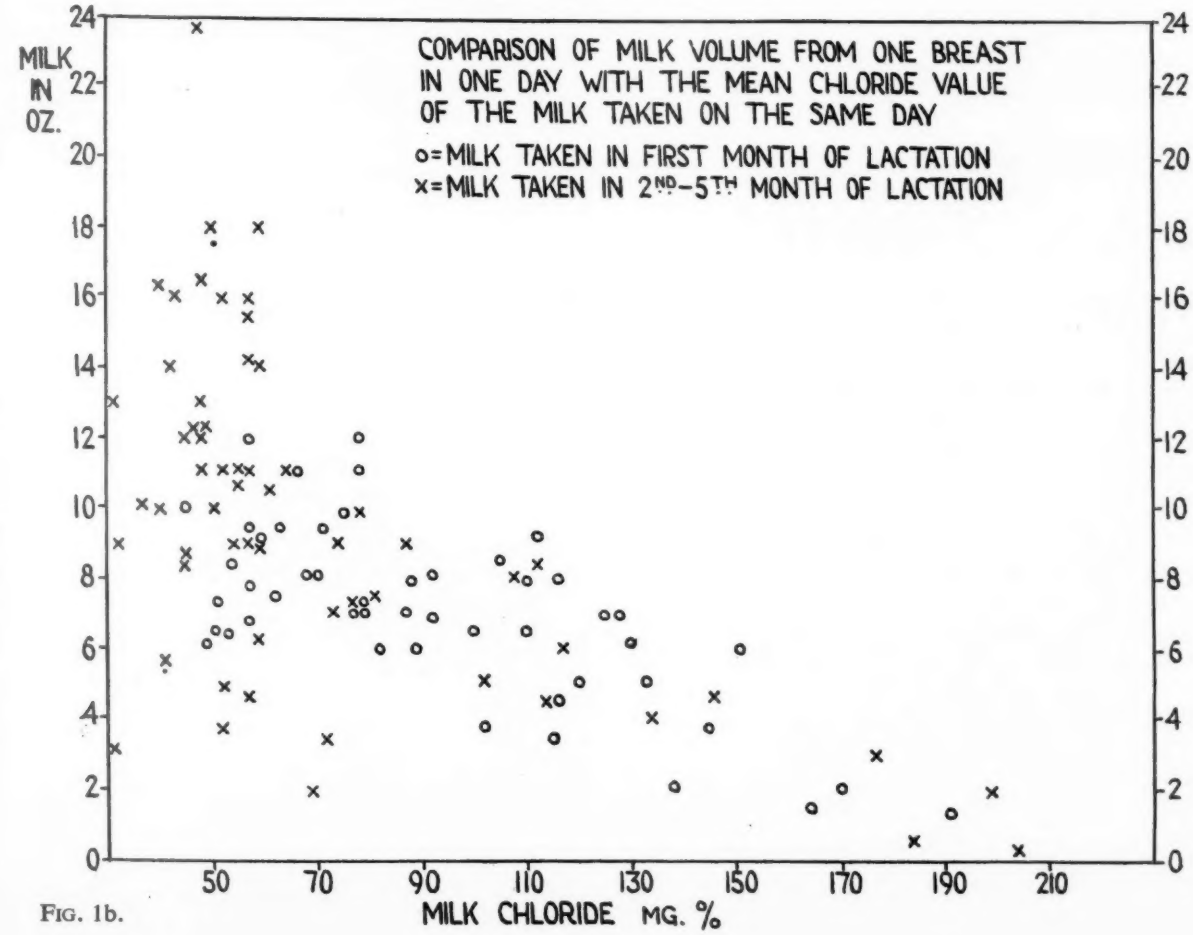
COMPARISON OF MILK VOLUME FROM ONE BREAST
IN ONE DAY WITH THE MEAN CHLORIDE VALUE
OF THE MILK TAKEN ON THE SAME DAY
o=MILK TAKEN IN FIRST MONTH OF LACTATION
x=MILK TAKEN IN 2ND–5TH MONTH OF LACTATION
MILK IN OZ.
MILK CHLORIDE MG. %
0
2
4
6
8
10
12
14
16
18
20
22
24
50
70
90
110
130
150
170
190
210

FIG. 1b.

in 4% of the women when the electrical conductivity measurement of their milk was compared with their milk yield and in 12% when the chloride content of their milk was compared with their daily milk yield. In each case the milk specimen was taken from a woman in the second to fifth month of lactation, and the milk yield from each of the affected breasts did not exceed 7 oz. though the conductivity or chloride value of that milk was relatively low. It is, therefore, apparent that such cases will be a source of error when interpreting the significance of the electrical conductivity and chloride values of milk in relation to milk yield.

### Relationship of Duration to Electrical Conductivity and Chloride Content in the First Month of Lactation

The electrical conductivity and chloride values of milk taken in the second to fourth week of lactation were correlated with the duration of lactation. The specimens of breast milk were obtained from 88 mothers in the second week of lactation and from 40 mothers in the third and fourth weeks of lactation. Each mother provided 4-8 ml. of milk before the 6 a.m. breast feed and a similar amount before the mid-day feed. The mean of the two conductivity values and of the two chloride values for each woman was calculated, and the duration of her lactation recorded.

### Results

The results are divided into three groups: one for mothers with milk with a conductivity value $150 \times 10^{-5}$ to $200 \times 10^{-5}$ ohm$^{-1}$ cm.$^{-1}$; another for mothers with milk with a conductivity value $201 \times 10^{-5}$ to $250 \times 10^{-5}$ ohm$^{-1}$ cm.$^{-1}$; and a third for mothers with milk with a conductivity value $251 \times 10^{-5}$ to $300 \times 10^{-5}$ ohm$^{-1}$ cm.$^{-1}$ (Table 2A). The number of mothers in each group is given. The number of mothers in each group lactating for one, two, three, four, and five months is stated as a percentage of the total number of mothers in the group (Fig. 2a).

The conclusions drawn from Table 2A and Fig. 2a are, first, that the lower the electrical conductivity of milk in the first month of life, the more likely is a mother to breast-feed her infant for five months, and, secondly, that the largest proportion of failures to breast-feed occur in the first two months of lactation. The former statement was shown to be statistically significant by applying the $\chi^2$ test to the data.

Additional information obtained from this investigation was that the 32 mothers who did not need to complement their breast feeds during the first five months of lactation had milk with a conductivity value of not more than $275 \times 10^{-5}$ ohm$^{-1}$ cm.$^{-1}$ during the second to fourth weeks of lactation, while women with a milk conductivity value about

TABLE 2A
CORRELATION OF ELECTRICAL CONDUCTIVITY AND DURATION OF LACTATION FOR WOMEN IN THE FIRST MONTH OF LACTATION

| Milk Conductivity × $10^5$ ohm$^{-1}$ cm.$^{-1}$ | Week of Lactation | Number of Mothers | Percentage Mothers* Lactating for | | | | |
|---|---|---|---|---|---|---|---|
| | | | One Month | Two Months | Three Months | Four Months | Five Months |
| 150–200 | 2 | 9 | 100 (9)† | 78( 7) | 67 (6) | 67 (6) | 67 (6) |
| | 3–4 | 10 | 100 (10) | 80 (8) | 80 (8) | 80 (8) | 80 (8) |
| 201–250 | 2 | 42 | 74 (31) | 53 (22) | 48 (20) | 34 (14) | 29 (12) |
| | 3–4 | 24 | 96 (23) | 63 (15) | 55 (13) | 55 (13) | 42 (10) |
| 251–300 | 2 | 38 | 58 (22) | 26 (10) | 21 (8) | 16 (6) | 11 (4) |
| | 3–4 | 5 | 80 (4) | 20 (1) | 20 (1) | 20 (1) | 20 (1) |

* Women in the second to fourth week of lactation, whose milk is of relatively low conductivity lactate, on the average, longer than those who have milk of a relatively high conductivity.
† Figures in brackets denote the number of mothers in the group.

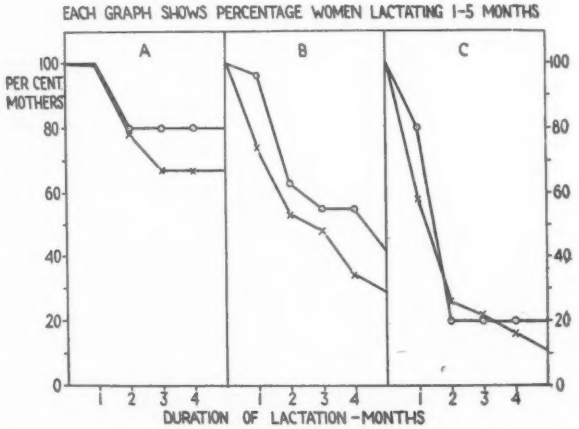


FIG. 2a.

$275 \times 10^{-5}$ ohm$^{-1}$ cm.$^{-1}$ in the second to fourth weeks of lactation found it necessary to give complementary feeds to their infants if they breast-fed them for five months.

The results of the chloride estimations are divided into three groups: 0 to 50 mg. %; 51 to 100 mg.%; and over 100 mg. % (Table 2B). The number of mothers in each group is given. The number of mothers in each group lactating for one, two, three, four, and five months is stated as a percentage of the total number of mothers in the group (Fig. 2b).

It may be seen, first, that the lower the chloride content of the milk in the first month of life, the more likely is a mother to breast-feed her infant for five months, and, secondly, that the largest proportion of failures to breast-feed occur in the first two months of lactation. The former conclusion was shown to be statistically significant by applying the $\chi^2$ test to the data.

The 32 mothers who did not need to complement their breast feeds during the first five months of lactation had a milk chloride value of not more than 110 mg. % during the second to fourth weeks of lactation. But women with a milk chloride value of more than 110 mg. % in the second to fourth weeks of lactation found it necessary to give complementary feeds to their infants if they breast-fed them for five months.

TABLE 2B

CORRELATION OF MILK CHLORIDE VALUES WITH DURATION OF LACTATION IN THE FIRST MONTH OF LACTATION

| Milk Chloride (mg. %) | Week of Lactation | Number of Mothers | Percentage Mothers* Lactating for | | | | |
|---|---|---|---|---|---|---|---|
| | | | One Month | Two Months | Three Months | Four Months | Five Months |
| 0–50 | 2 | 8 | 100 (8)† | 75 (6) | 63 (5) | 63 (5) | 63 (5) |
| | 3–4 | 7 | 100 (7) | 86 (6) | 75 (5) | 72 (5) | 72 (5) |
| 51–100 | 2 | 52 | 71 (37) | 47 (25) | 43 (22) | 33 (17) | 29 (15) |
| | 3–4 | 25 | 100 (25) | 68 (17) | 64 (16) | 64 (16) | 32 (13) |
| 101–150 | 2 | 28 | 61 (17) | 29 (8) | 25 (7) | 14 (4) | 7 (2) |
| | 3–4 | 8 | 63 (5) | 13 (1) | 13 (1) | 13 (1) | 13 (1) |

* Women in the second to fourth week of lactation, whose milk is of relatively low chloride content lactate, on the average, longer than those who have milk of a relatively high chloride content.

† Figures in brackets denote the number of mothers in the group.

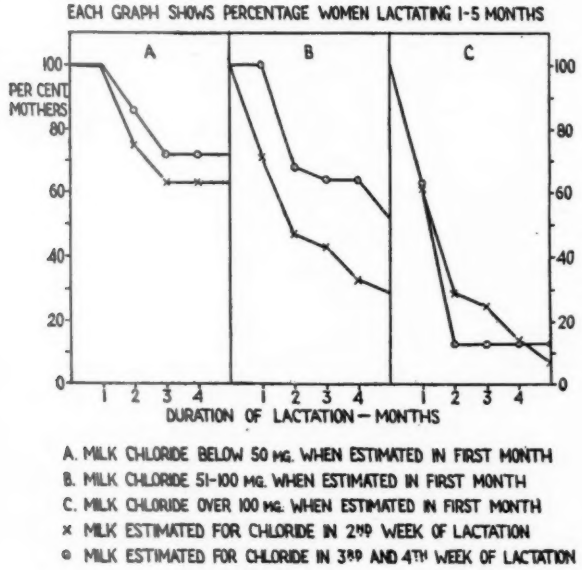


FIG. 2b.

## Discussion

When using either the electrical conductivity or chloride content of milk to predict the possible duration of lactation it is important to take into account certain abnormalities in the health of the mother which may occur during the first month of lactation and give rise to milk of either relatively high electrical conductivity (over $275 \times 10^{-5}$ ohm$^{-1}$ cm.$^{-1}$) or high chloride content (over 110 mg. %), because in these cases, if the abnormal condition subsides, lactation may proceed normally for five months. The first type of abnormality affected two mothers who had undergone Caesarean section. The establishment of breast feeding in these cases was delayed, partly due to the operation and partly to the fact that the babies were not put to the breast until they were 5 days old. The second type of abnormality was one involving the breasts. Here, breast feeding was interrupted in order to rest the breast for 48 hours. In one case this was because the mother had a cracked nipple, and in two other instances mastitis. In these patients the milk electrical conductivity and chloride values during the resting phase was high, but eventually lactation progressed normally. A third maternal condition, pyrexia, was associated with milk of relatively high

conductivity and chloride content in the second to fourth week of lactation, yet the mother so affected lactated satisfactorily on recovering normal health.


## Summary

The relationship of the electrical conductivity and chloride content of milk to daily milk yield was studied. Specimens of milk from apparently healthy women during the second week to fifth months of lactation were examined. From the results it was apparent that an inverse relationship existed between the average daily milk yield from one breast and both the electrical conductivity and the chloride content of the milk from that breast.

Low values obtained for milk were with few exceptions associated with high milk yields, while high values were usually accompanied by relatively low milk yields. However, with milk chloride values below 60 mg. % or electrical conductivity measurements below $210 \times 10^{-5}$ ohm$^{-1}$ cm.$^{-1}$ the milk yield might vary by as much as 20 oz. Therefore an accurate assessment of milk yield in ounces by either of these estimations was impossible. If, however, the electrical conductivity or the chloride content of the milk was relatively high, it was possible to calculate the milk yield in ounces with a fair degree of accuracy. Thus high milk values gave more accurate information regarding milk yield than low milk values.

In the second investigation, the electrical conductivity and the chloride content of milk taken in the second to fourth week of lactation were correlated with the duration of lactation. One hundred and twenty-eight cases were investigated, and the results of both the electrical conductivity measurements and the chloride estimations made on specimens from each woman were correlated with the duration of her lactation.

It was concluded from the second investigation that the electrical conductivity or chloride content of women's milk taken in the second to fourth week of lactation gave an indication of the probable duration of lactation.

The influence of the mother's health upon both the electrical conductivity and the chloride content of her milk was discussed.


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# A CASE OF FIBROCYSTIC DISEASE OF THE PANCREAS WITH INTESTINAL OBSTRUCTION

BY

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Fibrocystic disease of the pancreas was first described by Landsteiner in 1905, and it is of interest, that intestinal obstruction was one of the features of his case. Since then, and particularly in the past two decades, many well authenticated cases have been described.

Andersen (1938), described three clinical syndromes as being associated with essentially the same pathological lesion in the pancreas. The first was characterized by intestinal obstruction in the first week of life (meconium ileus); the second by respiratory infection in the first six months of life; and the third by the development of the coeliac syndrome in later childhood. The division into these types has been generally supported both by authors considering all phases of the disease (Andersen, 1939; Deem and McGeorge, 1941; Jeffrey, 1941; Wolman, 1942; Farber, 1942 and 1943; Markel, 1944; Menten and Middleton, 1944; Baggenstoss and Kennedy, 1945; Pugh, 1945; Andersen and Hodges, 1946; Bodian, 1946; Macgregor and Rhaney, 1948; Torgersen, 1948; Jones, 1949; Matheson, 1949; Andersen, 1949), and by those concerned only with meconium ileus (Dodd, 1936; Sobel, 1941; Sprenger, 1942; Farber, 1944a and b; Swenson and Ladd, 1945; Glanzmann, 1946; Hiatt and Wilson, 1948).

The case described here is remarkable for the occurrence of intestinal obstruction at the age of 7 months. It appears to be the first recorded instance in which this feature has developed so late in infancy.

### Case Report

J.R., a boy aged 9 weeks, was referred to hospital on February 29, 1949, from a welfare centre which the mother had attended because of feeding difficulties. The birth weight was 6 lb. 9 oz. and the infant had been breast fed. From the age of 3 weeks there had been a persistent, troublesome cough with attacks of diarrhoea and failure to gain weight. On admission the weight was 7 lb. 7 oz. The stools appeared green and undigested but pathogenic bacteria were not isolated on culture. The urine was normal and the haemoglobin 76% (Haldane). Stool examinations were negative for trypsin, and radiographs of the chest showed catarrhal changes in both lungs. The diagnosis of fibrocystic disease of

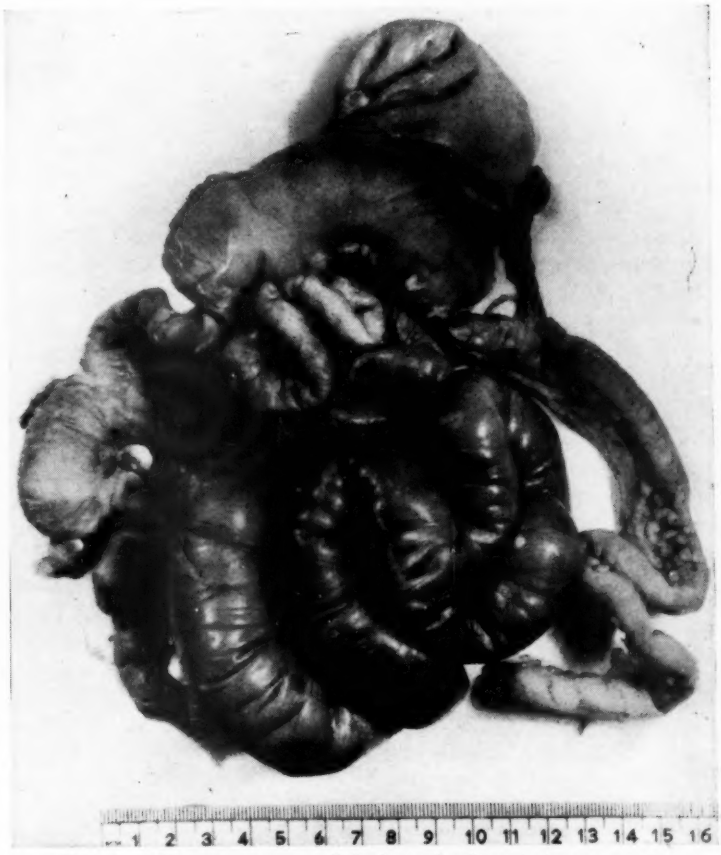


FIG. 1.—The appearance of the intestinal tract at necropsy.

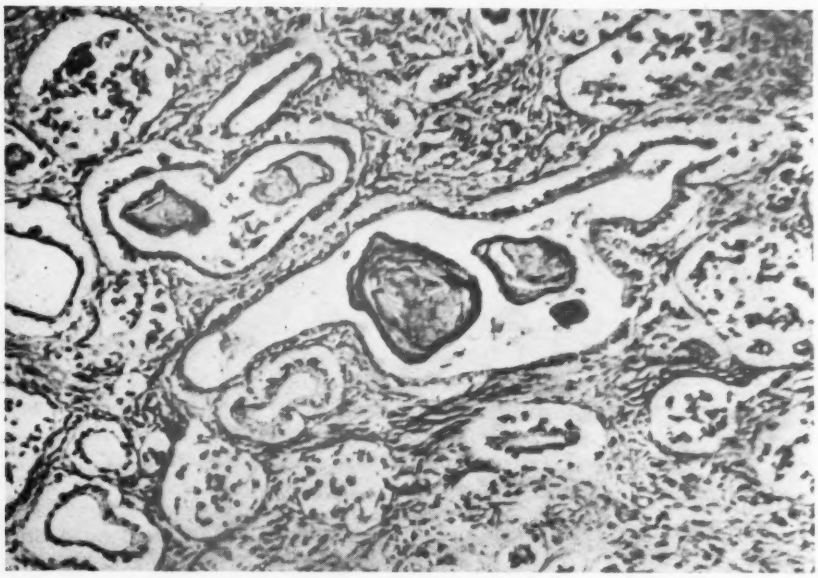

FIG. 2.—Section of the pancreas (Mallory's fibrous tissue stain. × 110).

the pancreas was made and the patient was discharged home. Breast feeding was continued until the age of 5 months when weaning began, and pancreatin (gr. 60 daily) was given throughout. Courses of penicillin were given on three occasions for exacerbations of the respiratory infection. Progress was satisfactory from the age of 4 months up to the terminal episode. The patient was readmitted to hospital on April 11, 1949, with a history of having vomited all feeds during the previous three days and absence of bowel action for four days. A tentative diagnosis of intussusception was made and an immediate laparotomy was performed. A small amount of straw-coloured fluid was present in the peritoneal cavity. The small gut was plum-coloured and distended, and there were haemorrhages at the root of the mesentery; the colon was contracted and empty. No cause for obstruction could be found, and the abdomen was closed without further interference. Convulsions occurred after the operation and the patient lapsed into coma and died the next day.

**Post-mortem Findings.** The peritoneal cavity contained a small amount of fluid, and there were delicate fibrinous adhesions between the loops of bowel. The small intestine was distended and plum-coloured to within 12 cm. of the ileo-caecal valve. Small haemorrhages were present in the mesentery and the contents of the distended gut were of a putty-like consistency. There was no evidence of volvulus, intussusception, or other organic obstruction. The transverse colon showed some gaseous distension but the remainder of the large bowel appeared collapsed (Fig. 1). The pancreas was somewhat firmer than normal, but the main pancreatic and bile ducts were patent. Apart from some pallor of the liver and kidneys the other organs were essentially normal. There was no evidence of bronchiectasis.

Histological examination of the pancreas showed a great increase in fibrous tissue, the acini being split into small groups by broad bands of collagen. Cystic dilatation of the ducts was marked, and many contained desquamated epithelium and homogeneous eosin-staining material (Fig. 2). The clinical diagnosis of fibrocystic disease of the pancreas was thus confirmed. Histological changes in other organs were of a minor character and not relevant to this discussion. A histological examination of the gut was not made.

## Discussion

In the Table a summary is given of the recorded cases of fibrocystic disease of the pancreas associated with intestinal obstruction and supported by post-mortem and histological studies. The cases of congenital intestinal obstruction reported by Torkel (1905), Bullowa and Brennan (1919), Hughes (1922), Exalto (1924), Meltzer (1936), Burger (1938), and Adamson and Hild (1939) have not been included. Although some of these may have been due to fibrocystic disease of the pancreas, histological proof is lacking. Other reported cases have been excluded as the available evidence points to a different underlying pathology (Soldin, 1913; Fanconi, 1920; Frick, 1934; Denzer, 1941; Jeffrey, 1941—second case; Sprenger, 1942—first case; and Hinden, 1950).

All the 55 accepted cases included in the Table occurred in the neonatal period; the obstructive element in all is therefore covered by the term meconium ileus. The presence of associated volvulus (cases 17, 41, 43, 44, and 54) can certainly be regarded as a secondary manifestation, and the presence of congenital bands (cases 4, 18, 42, and 46) as coincidental. However, it is interesting to note the high incidence of atresia of the small gut, no fewer than nine of the 55 cases showing this abnormality (cases 5, 6, 10, 13, 14, 21, 24, 49, and 55). Andersen (1938) considered that such atresia was coincidental, but Zuelzer and Newton (1949) suggested that it was the direct result of the meconium ileus. They receive strong support from Lelong, Petit, Le Tan Vinh, and Borniche (1950) who produced striking histological evidence from examination of the intestinal wall in their case. They found replacement of the mucous membrane and muscle layers by granulation tissue which led to scar formation and secondary atresia.

In the case recorded here the only cause for the

TABLE

RECORDED CASES OF PROVED FIBROCYSTIC DISEASE OF THE PANCREAS WITH INTESTINAL OBSTRUCTION

| Case No. | Author | Age at Onset | Associated Abnormalities |
|---|---|---|---|
| 1 | Landsteiner, 1905 | Birth | |
| 2 | Kornblith and Otani, 1929 | 2 days | |
| 3 | Dodd, 1936 | Birth | |
| 4 | Andersen, 1938 | Neonatal | Fibrous band |
| 5 | | Neonatal | Atresia small gut |
| 6 | | Neonatal | Atresia small gut |
| 7 | Blackfan and May, 1938 | Neonatal | |
| 8 | | Neonatal | |
| 9 | | Neonatal | |
| 10 | | Neonatal | Atresia small gut |
| 11 | | Neonatal | Cirrhosis of liver |
| 12 | Bronaugh and Lattimer, 1940 | Birth | |
| 13 | Deem and McGeorge, 1941 | Congenital | Atresia small gut |
| 14 | | Congenital | Atresia small gut |
| 15 | Sobel, 1941 | Birth | |
| 16 | Jeffrey, 1941 | Neonatal | |
| 17 | Hurwitt and Arnheim, 1942 | Birth | Volvulus |
| 18 | Flax, Barnes, and Reichert, 1942 | Birth | Fibrous band |
| 19 | Sprenger, 1942 | Birth | Meckel's diverticulum |
| 20 | Kaufmann and Chamberlin, 1943 | Birth | |
| 21 | Menten and Middleton, 1944 | Birth | Atresia small gut |
| 22 | Baggenstoss and Kennedy, 1945 | Neonatal | |
| 23 | Wissler and Zollinger, 1945 | Birth | |
| 24 | Bodian, 1946 | Neonatal | Atresia small gut |
| 25 | | Neonatal | |
| 26 | | Neonatal | |
| 27 | Glanzmann, 1946, and Riniker, 1946 | Birth | |
| 28 | Andersen and Hodges, 1946 | Neonatal | |
| 29 | | Neonatal | |
| 30 | | Neonatal | |
| 31 | | Neonatal | |
| 32 | | Neonatal | |
| 33 | Hiatt and Wilson, 1948 | 1 day | |
| 34 | | Birth | |
| 35 | | Birth | |
| 36 | | Birth | |
| 37 | | 2 days | |
| 38 | | 2 days | |
| 39 | | 2 days | |
| 40 | | 1 day | |
| 41 | Andersen (unrecorded cases quoted by Hiatt and Wilson, | 2 days | Volvulus |
| 42 | 1948) | 3 days | Peritoneal bands |
| 43 | | 1 day | Volvulus |
| 44 | | 1½ days | Volvulus |
| 45 | | 2 days | |
| 46 | | 2 days | Peritoneal bands |
| 47 | | 4 days | |
| 48 | Macgregor and Rhaney, 1948 | Birth | |
| 49 | Zuelzer and Newton, 1949 | Birth | Atresia small gut |
| 50 | | Birth | |
| 51 | | Birth | |
| 52 | | Birth | |
| 53 | | Birth | |
| 54 | Glanzmann and Berger, 1950 | Birth | Volvulus |
| 55 | Lelong *et al.*, 1950 | Birth | Atresia small gut |

intestinal obstruction was the abnormal state of the intestinal contents. Farber (1944b) stated that meconium ileus without pancreatic disease might be due to volvulus, stenosis of the ileo-caecal valve, or biliary obstruction: none of these causes was operative in the present case. Analysis of the intestinal contents found at necropsy gave normal figures for total and split fat (total fat 55·3 g. per 100 g. dried faeces; 74% of the fat was split). The usual findings in this disease are increased total fat with a high percentage of unsplit fat (Shohl, May, and Shwachman, 1943; Andersen, 1945). Moreover the stools had not been bulky or malodorous. The absence of such abnormalities may not be surprising in view of the continuous administration of pancreatin for the four months before death. A high faecal nitrogen content is also characteristic of this disease (Shohl *et al.*, 1943), but owing to the rapidity with which death took place in the terminal episode no other biochemical studies were carried out. Despite the failure to correlate the altered physical state of the intestinal contents with any specific chemical abnormality, it is reasonably certain that the alteration in this case must be ascribed to the pancreatic lesion.

It is universally agreed that in meconium ileus the obstruction is the direct result of the abnormal physical character of the meconium. Further, in cases uncomplicated by obstructing bands, atresia or volvulus, the morbid anatomical picture is uniformly that of a distended ileum only slightly affecting the terminal loop, and a contracted empty large bowel (Dodd, 1936; Sobel, 1941; Sprenger, 1942; Kaufmann and Chamberlin, 1943; Farber, 1944b; Riniker, 1946). Except for the age of the patient the case recorded here closely parallels the features of meconium ileus. There are the same lesion in the pancreas, a similar change in the physical character of the intestinal contents, and an identical morbid anatomical picture.

Farber (1942, 1944a and b) pointed out that pancreatic achylia in the late intra-uterine period causes meconium ileus, whereas if it develops later in life it produces the coeliac syndrome. It should not be surprising, therefore, that two clinical conditions resulting from the same basic pathological lesion show close similarity although occurring at different ages.

Hiatt and Wilson (1948) in discussing meconium ileus suggest that all gradations occur from partial or subacute obstruction to complete obstruction, and that in some cases obstruction is relieved spontaneously by the passage of meconium plugs. It seems clear that there is a transition from the cases occurring early in infancy in which the obstructive features predominate (meconium ileus) to the cases developing later in which the features of steatorrhoea (the 'coeliac syndrome') dominate the clinical picture. The difference in the clinical features at the different ages is no doubt related to the increased muscular vigour, including the power of intestinal peristalsis, in the older children. In these more vigorous children the bowel is capable of propelling the putty-like faeces through the ileo-caecal valve, but even in these cases intestinal stasis develops and may well be responsible for the vomiting which is such a prominent clinical feature. It is in the younger and more debilitated cases that complete obstruction is liable to supervene.

Rasor and Stevenson (1941) describe a boy with fibrocystic disease of the pancreas who died at the age of 1 year with a combination of respiratory infection and coeliac syndrome. Vomiting was a particularly troublesome feature, and at necropsy the intestinal contents were found to be of a putty-like consistency. Unfortunately most authors do not stress the putty-like character of the intestinal contents in similar cases. It seems likely that such a faecal abnormality is common in the coeliac phase of fibrocystic disease of the pancreas.

In the case recorded here intestinal obstruction developed at the unusually late age of 7 months when the patient had already entered the coeliac phase of the disease, a phase rarely encountered before the age of 1 year. The case thus forms a link between the classical 'meconium ileus' of the neonatal period and the coeliac phase of later childhood. The possibility of intestinal obstruction at this age, even when volvulus is present, being due to an altered physical state of the bowel contents with fibrocystic disease of the pancreas as its underlying pathology, should be borne in mind.

**Summary**

A case of fibrocystic disease of the pancreas is described. The patient died from intestinal obstruction at the age of 7 months.

The relation between meconium ileus and the coeliac phase of this disease is discussed.

Attention is drawn to the possibility of overlooking fibrocystic disease of the pancreas as a cause of intestinal obstruction after the first few days of life.

The literature on fibrocystic disease of the pancreas with intestinal obstruction is reviewed.

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# PHAEOCHROMOCYTOMATA IN CHILDREN

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The occurrence of a phaeochromocytoma in a child has not apparently been reported in the English literature. There are now reports in the world literature of at least 14 cases in children under the age of 14 years in whom the diagnosis was made during life. Twelve of these children were operated upon; nine of them were cured by surgery but three died.

Cahill (1948) has operated on three such children, and in two of his cases the operation was successful. In one case, a tumour was discovered at operation in a child of 2 years of age (Neff, Tice, Walker, and Ockerblad, 1942), but the other 13 children were between the ages of 10 and 15 years when the diagnosis was made. It is, however, notable that although the diagnosis in these 13 children was not made until after they were 10 years old, yet in ten of them the symptoms had begun between the ages of 6 and 8 years. With increasing awareness of the symptom-complex, it may be assumed that diagnosis will be made earlier with an improved chance of survival for these children.

Hypertension in children occurs in renal disease, in acrodynia (pink disease), in coarctation of the aorta, in lead poisoning, and in phaeochromocytomata. These diseases can usually be differentiated by clinical and laboratory examination, and the diagnosis of phaeochromocytomata in children should be easier than it is in adults in whom the distinction from essential hypertension constitutes a major diagnostic problem. Where renal failure supervenes on hypertension, the distinction from primary renal disease is undeniably difficult in children as in adults, and in one reported case in a child, this caused considerable delay in making the diagnosis of phaeochromocytoma (Koffler, Buck, Wingard, Hitchcock, Guthrie, and Teague, 1950).

The following case report concerns a boy who had four tumours, one in each adrenal, and two smaller ones in the para-aortic chromaffin tissue, and who died following a laparotomy.

## Case Report

M.B., aged 11½, was admitted to the wards of the Derbyshire Hospital for Sick Children on August 3, 1950, from the Out-patient Department, where he had been referred by his doctor, Dr. G. S. N. Dow, for an opinion on his cardiac condition. The history of his illness went back to the age of 6½ years, when he began to have recurrent attacks of acute abdominal pain, accompanied by vomiting. His family doctor noted that the attacks of pain were associated with great sweating, and that while the attacks were occurring the pulse rate was very rapid, and the temperature was raised to 99°. The high pulse rate was not maintained after the attack, but there was a persistent systolic murmur in the mitral area. Attacks of sweating also occurred unassociated with pain. In June, 1945, he developed intermittent nocturnal enuresis.

He complained of pain in the eyes and photophobia in February, 1946, and he was seen by Mr. T. E. A. Carr, and later also by Mr. C. H. Bamford in consultation. Mr. Carr's report on January 26, 1946, is as follows:

'Pupil reactions normal: R.V.=6/60 L.V.=6/60. Right fundus, massive exudate at posterior pole involving disc of which the position can only be located by the direction of the larger retinal vessels, which are themselves largely obscured by the very unusually dense exudate. There are a few small outlying patches of exudate. Down and out, old (inactive) patches of scar tissue with pigment deposits can be seen.

'Left fundus, similar to right, but the massive exudate is mostly to the nasal side of the disc, of which the form can be made out fairly well. Old scars (fibrotic and pigmented) are seen temporarily. There was no sign of vascular disease in the fundi.'

In view of the ophthalmological suggestion that papilloedema might be concealed by the massive exudate, the child was admitted for lumbar puncture and radiography of the skull. X-ray examination was negative. The pressure of the cerebrospinal fluid appeared normal, but there was insufficient for actual measurement; examination of the fluid showed eight polymorphonuclear cells and 22 lymphocytes with 66 mg. % protein.

He was observed in the Out-patient Department until June, 1947, when he ceased to attend. During this time, his attacks of abdominal pain ceased, and his general condition improved; he gained 9 lb. (weight, 56 lb. at the

age of 8). The retinal lesion was noted to be regressing, the exudative retinopathy disappeared, and some of the fibrous scars had cleared. There were white areas suggestive of choroidal sclerosis, and a few small patches of pigment were seen in each retina with some pale spots at each macula. Vision was 6/60 in the right eye and less than 6/60 in the left.

During the following three years he did not attend the hospital, but he was stated by his parents to have been very well, and to have attended school regularly. He had, however, continued to be nervous, and sweated a great deal. He was very active, but on occasional days he appeared fatigued. He was taken to see Mr. Affleck Greeves in July, 1949, who, in December, 1950, gave this retrospective opinion concerning his findings in the light of the subsequent diagnosis.

'I find it difficult to associate the fundus changes in this case with the presence of a phaeochromocytoma, with the exception of the narrowing of the retinal arteries which was extremely evident. The changes were primarily choroidal, and without any signs of recent activity. They consisted of fairly extensive atrophic patches in the choroid, such as one finds as the result of a severe inflammatory affection, and there was in addition an organized strand of old inflammatory exudate in the right macula. It is true that in one of Bruce's cases two minute areas of old choroiditis were observed in one eye in addition to the retinopathy, but in my opinion these were not necessarily of any significance, because such patches are frequently found in the peripheral fundus of otherwise perfectly normal eyes.'

**Examination and Investigation.** The boy was both restless and active; he was usually pale, but when under examination his face, hands, and feet became a bright red. He would then sweat profusely. His intake of fluid varied between 3 and 5 pints daily, and his output between 20 and 35 oz. daily. It was not thought that his consumption of food was excessive. His weight was 71 lb. (a gain of 19 lb. in the previous three years), and his height 4 ft. 7½ in. Pubic and axillary hair was beginning to grow. His temperature was normal, subnormal, or was sometimes between 99° and 100°.

An examination of the cardiovascular system showed that his pulse rate varied between 96 and 130 a minute. His heart was enlarged, the apex beat was in the fifth space in the anterior axillary line. There was a systolic thrill at the apex. There was a loud systolic mitral murmur, a rough systolic murmur at the base, maximal in the aortic area and conducted into the neck, and a diastolic murmur conducted down the sternum. The brachial, radial, and femoral arteries appeared hard, and there was good pulsation in the femoral arteries. The blood pressure taken on scores of occasions varied between 150 to 240 systolic and 100 to 130 diastolic.

The heart shadow portrayed a large heart, and the enlargement in both the postero-anterior view and the second oblique view was demonstrated to be due to the left ventricle (Figs. 1 and 2). The aorta was unfolded, but there was no calcification. There was no notching of the ribs and no pulmonary congestion.

The retinoscopy showed a few areas of fibrosis and pigmentation in both fundi. The retinal arteries were extremely attenuated.

The sodium amytal test (Fig. 3), grains 1½ repeated twice at one-hour intervals, gave no evidence of marked lability of blood pressure.

In the benzodioxane (piperoxane hydrochloride) test (Fig. 4), M.B. required 12 mg. (The dose of benzodioxane is calculated on the surface area of the patient, the usual adult dose being 20 mg. The patient is put under the basic conditions, and an intravenous normal saline drip is set up. Twenty to 30 minutes is allowed for the blood pressure to become stabilized, then three blood pressure readings are recorded at intervals of two to three minutes. The last readings are taken 1 minute and 30 seconds before injection of the benzodioxane. The solution is injected slowly over two minutes. After the injection, the blood pressure is taken at one-minute intervals for 10 to 15 minutes. If the hypertension is associated with an adrenaline-producing chromaffin tumour, a drop of 20 to 50 mm. in both diastolic and systolic pressures occurs within four minutes, while the pressure returns to its pre-injection levels in about 15 minutes.) The positive result in M.B. is shown in the graph (Fig. 4).

The electrocardiograms (Fig. 5) showed an inversion of T waves in the classic leads II and III, while in the unipolar chest leads there was inversion of the T waves in all leads, indicative of left ventricular strain.

The urine showed no albumen, red cells, or casts. The blood urea was 35 mg. % and urea clearance showed 105% of normal function. The urine concentration and dilution test was normal (1022-1002).

The intravenous pyelograms were normal except for some slight distortion of the superior calyx on the left side.

The perirenal insufflation of air (Fig. 6) produced good pictures only of the left renal area (Mr. A. J. Wilson and Dr. G. Q. Chance). During this examination the boy became ill with symptoms we had learnt to recognize as hyperadrenalinism—sweating, tachycardia, rise of blood pressure, and collapse—which required the discontinuance of the examination. There was an area of increased density in the left kidney above the superior calyx. This shadow was not regarded as sufficiently diagnostic of a tumour to justify exploration of the left adrenal, especially in view of the failure on the right side.

An examination of his carbohydrate metabolism showed that there was transient glycosuria, and the fasting blood sugar level was 140 mg. %. The glucose tolerance curve after 50 g. of glucose showed:

| | |
|---|---|
| ½ hour .. .. .. | 165 mg. % |
| 1 hour .. .. .. | 165 mg. % |
| 1½ hours .. .. .. | 120 mg. % |
| 2 hours .. .. .. | 120 mg. % |

The blood count was as follows: Hb. 108%, R.B.C.s 4,990,000 per c.mm., C.I. 1·1, W.B.C.s 16,000 per c.mm. (eosinophils 3%, old metamyelocytes 8%, neutrophils 73%, lymphocytes 15%, monocytes 1%). Red cells and platelets were normal.

Dr. A. M. Hain, of the Department of Obstetrics and Gynaecology, University of Manchester, on September 3, 1950, made the following report:

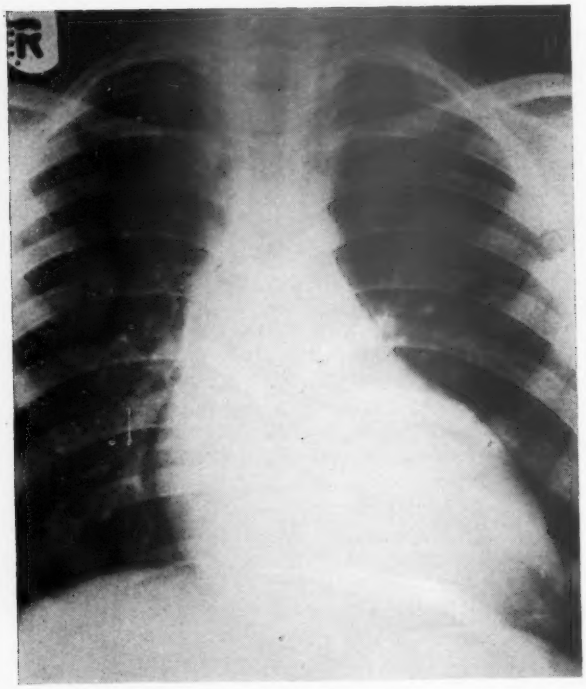

FIG. 1.

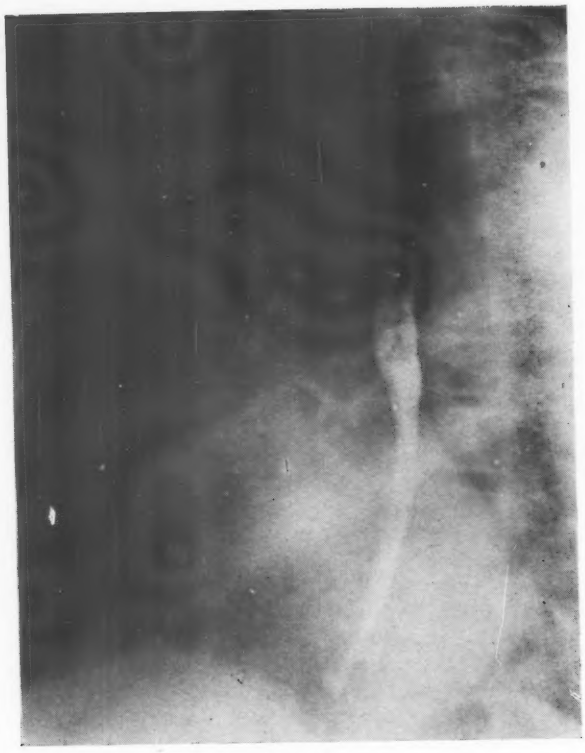

FIG. 2.

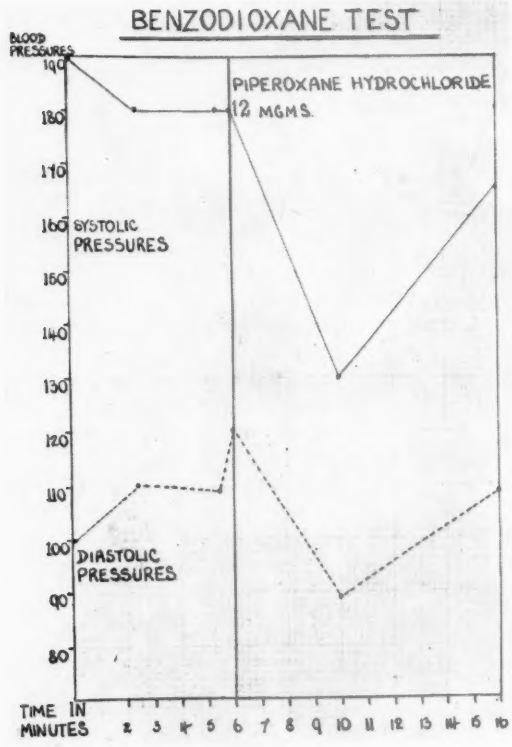


FIG. 4.

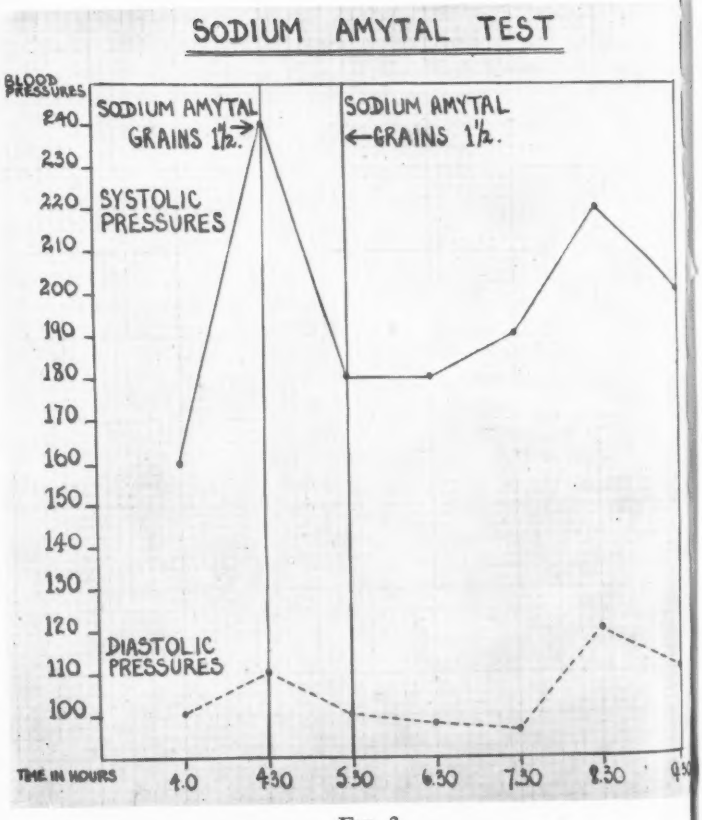


FIG. 3.

FIG. 1.—Heart shadow showing left ventricular enlargement.

FIG. 2.—Barium swallow in left-oblique position showing left ventricular enlargement.

FIG. 3.—Graph showing response of blood pressure to sodium amytal.

FIG. 4.—Graph showing response of blood pressure to benzodioxane.

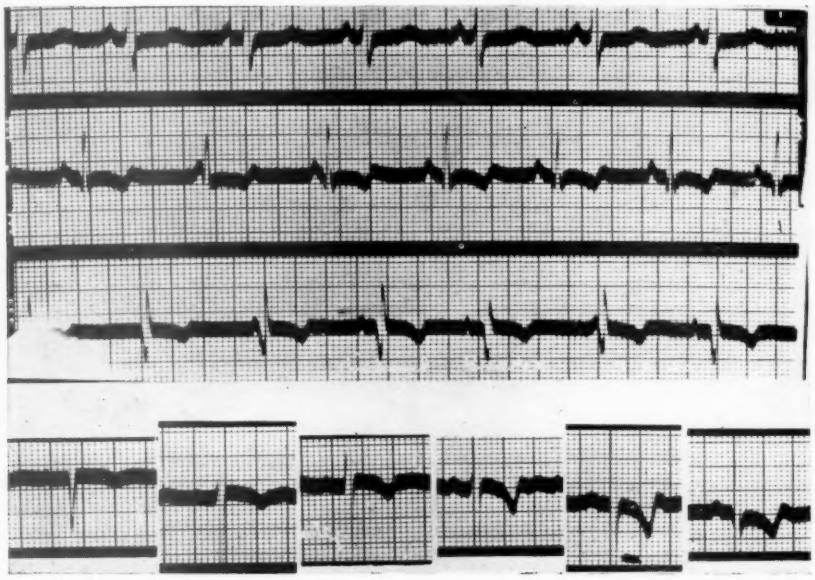

FIG. 5.—Electrocardiograms of leads I, II, III and V, I-VI. Inverted T Waves in leads II and III and V, I—VI. Left axis deviation with vertical heart.

'17-Ketosteroids, 3·7 mg. in 24 hours; gonadotrophins, merely a trace (about 2 or 3 M.U. in 24 hours). These values suggest hypopituitarism, as both of them are low for a boy who is nearly 12 years old. He should be excreting about 5 or 6 mg. of 17-ketosteroids in 24 hours.'

All other investigations, including cerebrospinal fluid and radiography of the skull, were normal.

**Diagnosis.** A diagnosis of phaeochromocytoma producing hypertension, arteriosclerosis, and coronary ischaemia was made with confidence on these findings. In view of the comparative failure of the x-ray examination by perirenal air, it was decided that a diagnostic laparotomy should be made. This was done on September 13, 1950, by Mr. A. J. Wilson under gas, oxygen, and 10 mg. of curare, given by Dr. R. Bliss. The blood pressure before the operation was 180 systolic, 110 diastolic. It rose to 220/154 during the induction.

A hard tumour was discovered in the right adrenal, and a suspicious smaller tumour was felt apparently in the area of the tail of the pancreas. The cardiac rate increased from 160 in the induction period to 180 per minute during the operation. While the tumour on the left side was palpated, the pressure rose to 230/170, and while the tumour on the right side was palpated, the pressure rose to 236/180. At the end of the operation, the pressure was 220/140, and the heart rate was 164 per minute. It was intended that the tumour (or tumours) should be removed at a later date. However, this intention was prevented as the boy died seven hours after the operation. His blood pressure rose to 210/150 again one hour after the operation, but thereafter fell steadily to 150/110 rising to 160/130 half an hour before death. His pulse rate varied between 140 and 160 per minute. He was conscious, cooperative, and not cyanosed during this time, and was taking fluids by mouth. He became unconscious with muscular twitching at 5 p.m., and died 10 minutes later. His death was presumably the result of vasomotor stress upon a cardiovascular system already damaged by hyperadrenalinism.

**Necropsy Report.** Necropsy was performed by Dr. I. Mackenzie on September 14, 1950, 17 hours after death.

The meninges were normal. There was a fair degree of atheroma in the vessels at the base of the brain, but the brain showed no organic disease apart from hyperaemia.

Examination of the cardiovascular system showed that there was an enlarged pericardial cavity containing a large heart, but no excess of fluid. The weight of the heart empty was 14½ oz. The valves were functionally competent. There was marked hypertrophy of the left ventricular wall, the muscle being of apparent good quality and 3 cm. in thickness. Atheroma was present in the coronary vessels and could

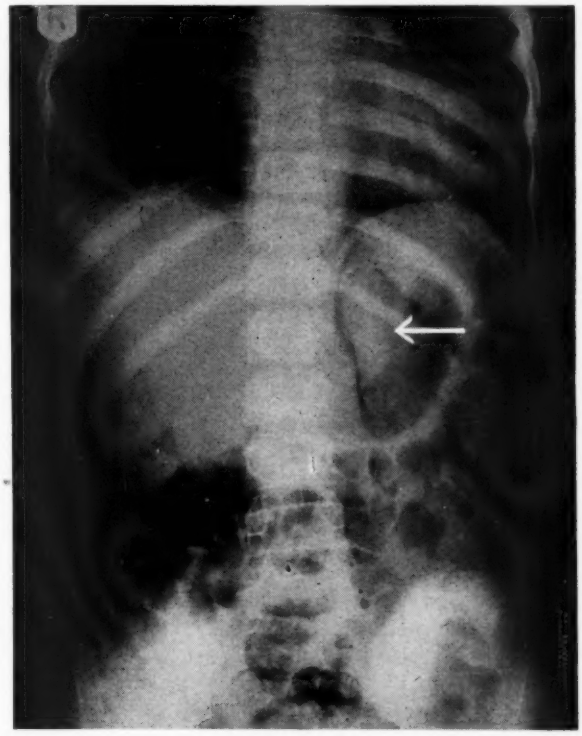

FIG. 6.—Perirenal insufflation of air showing an area of increased density over superior calyx in the left kidney.

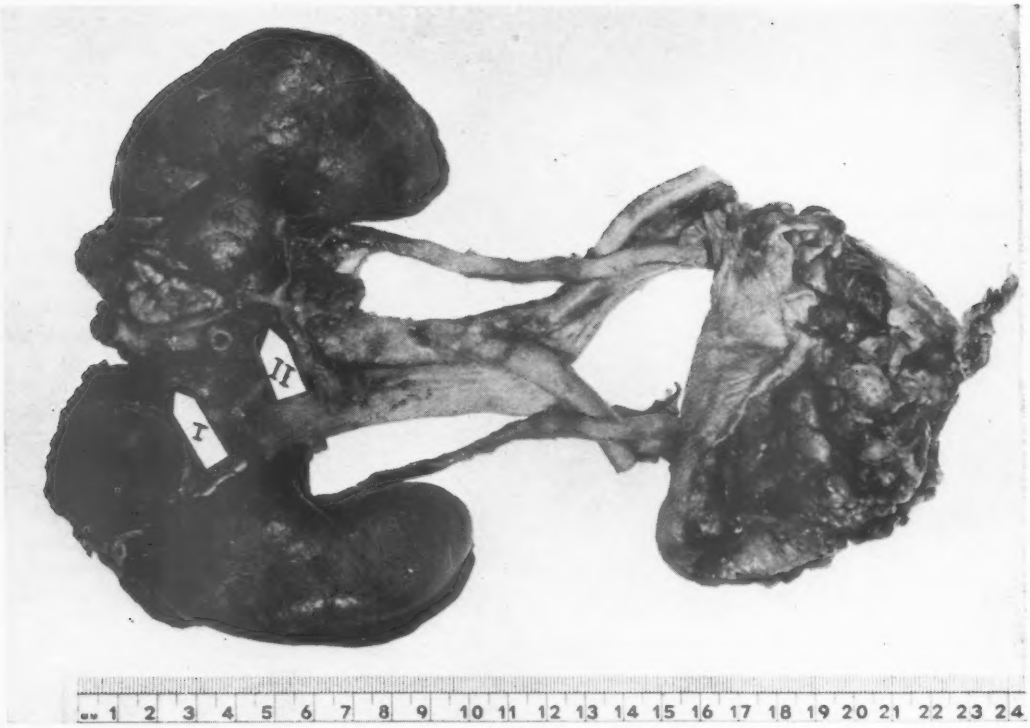


FIG. 7.

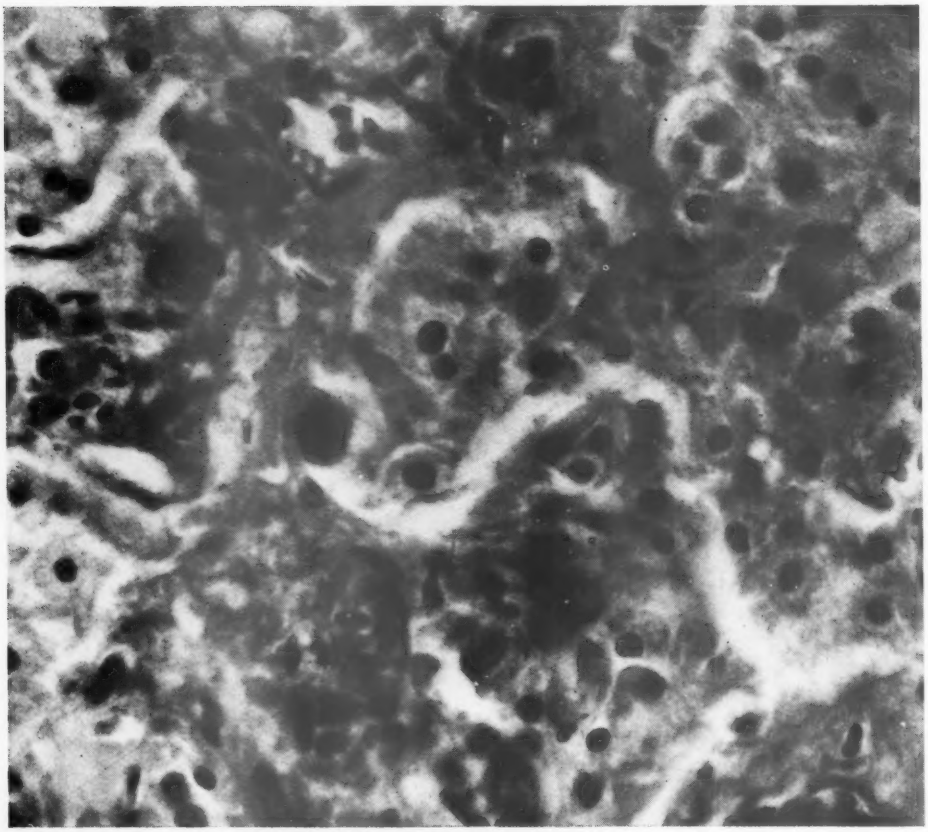

FIG. 8.

FIG. 7.—Specimen showing four tumours, one in each gland and two smaller ones along the aorta labelled I and II.

FIG. 8.—Section of phaeochromocytoma showing a ganglion cell. × 180.

be discerned by the naked eye, but there was a considerable degree of atheromatous change in the carotid and aorta. The iliac arteries were hard even to the touch.

In the adrenals there was a tumour present in each gland. The right tumour was roughly spherical and measured 3 × 3 × 2·8 cm. in its widest measurement. It had a pale grey-red centre and appeared to be encapsulated. The centre was continuous with the chromaffin tissue in the medulla of the remnants of normal adrenal gland. This tumour was situated at the upper aspect of the adrenal. The left adrenal tumour was more ovoid in shape, and was confined to the lower pole of the adrenal in coming over the upper pole of the kidney and half of the renal pelvis. It was 2·8 cm. in its widest measurement and 1·6 cm. in its narrowest. There was very little adrenal tissue of normal appearance on the left side. The tumours had the naked eye appearance of phaeochromocytomata. There were also at least two accessory tumours of similar nature, one situated on the anterior aspect of the aorta on the right side in close relation to the right adrenal tumour, and another on the anterior aspect of the aorta. A search was made for the organ of Zuckerkandl and for other remnants of chromaffin tissue around the aorta and along the carotid vessels, but none was found (Fig. 7).

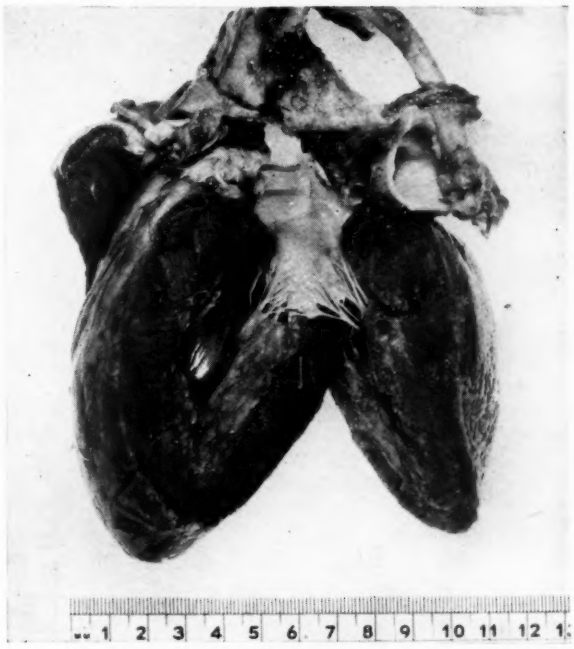


FIG. 9.—Heart showing hypertrophied left ventricle.

**Histological Examination.** Microscopically the tumour consisted of loose bundles of cells lying in close relation to vascular channels supported by firm fibrovascular stroma (Fig. 8). The cells were mainly spherical in shape and fairly uniform in size. Some cells were polyhedral, and others had ill-defined borders, but the nuclei were comparatively large and stained well. No mitoses were seen. There was a faint attempt at acinar grouping of the cells, but few collections were to be observed in such formation. The chromaffin reaction was exhibited in many cells. This consists of brown granules within the cytoplasm of certain of the chromaffin cells in bichromate fixed tissue. It was visible not only in unstained sections, but could be seen in the haematoxylin and eosin and Giemsa-stained slides. It showed to advantage in the latter. Not all the typical cells showed these granules, and the intensity of granule formation varied from cell to cell in those which did stain. There were certain cells which showed a resemblance to sympathetic ganglion cells, but distribution was not general throughout the tissue. The fibrovascular stroma was very well marked, and all the bundles of cells lay in close relation to capillaries. One area of the tumour was particularly richly supplied with vessels. Many large arteries could be discerned running through the tissue. The fibrous stroma was also well developed, and was accompanied by an increase in both pericellular and periacinar reticulin (Fig. 9).

Sections of the myocardium showed typical hypertrophy (Fig. 9) of the muscle as in hypertensive heart disease, and the vessels running in the myocardium showed advanced subintimal proliferation and reduplication of elastic tissue (Fig. 10). The anterior descending branch of the left coronary artery showed formation of atheroma accompanied by necrosis in the deeper part of the subintimal layer. Vessels containing cholesterol clefts were frequent and accompanied by a great reduction in the size of the lumen of the vessel (Fig. 11). The coronary vessels also showed reduplication of elastic tissue. The carotid arteries and aorta showed similar changes of lesser intensity, and this change was also present in the splenic arterioles although the spleen showed no gross lesion other than passive venous congestion.

The kidneys did not appear to be extensively involved, the main lesions consisting of a prominence of the glomerular lining membrane and a mild degree of tufting of the unit. There were, however, certain glomeruli filled with red cells, and showing focal embolic nephritis. Others showed advanced necrosis with a fibroblastic reaction in the surrounding renal parenchyma.

The arteries showed moderate subintimal hypertrophy which was continued down into arterioles. The cause of the focal embolic lesions appeared to be essentially vascular, and might have been entirely due to local increase in subintimal hypertrophy in an arteriole (Fig. 12). The sections of the eye showed signs indicating old haemorrhagic exudate in the subchoroid layer (Fig. 13). There were many macrophages around the vessels containing haemosiderin. There were one or two small areas of imperfect calcification or bone formation near the scleral junction, and this indicated former disease in this vicinity. There was also the possibility of a subretinal exudate having occurred in this eye, reduced by the fact that this was an eye removed at necropsy and the changes might be due to inadequate fixation. The vessels, however, showed marked reduplication of the elastic lamina similar to those obtaining in the carotid and coronary arteries. The adrenal cortex was normal, all three zones being well differentiated.

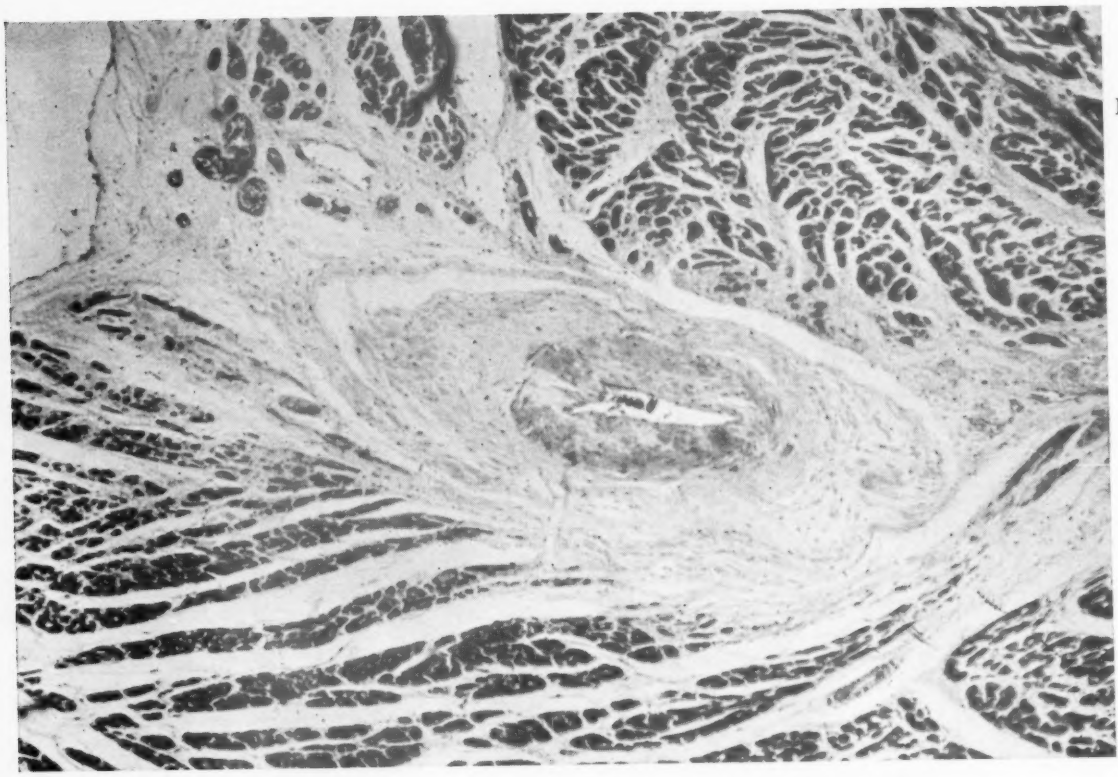

FIG. 10.

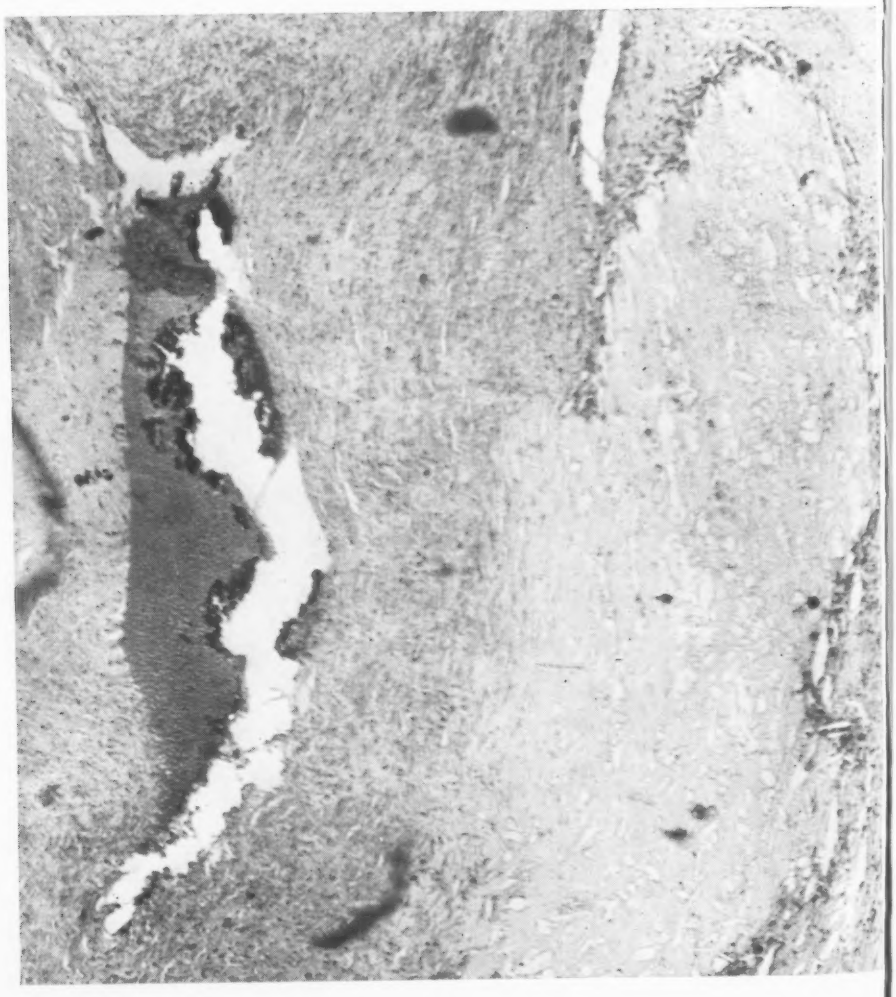

FIG. 11.

FIG. 10.—Hyperplastic arteriole in myocardium. × 200.

FIG. 11.—Anterior branch of left coronary artery showing numerous cholesterol clefts and subintimal hyperplasia. × 150.

FIG. 12.—Focal embolic nephritis showing glomerulus stuffed with red cells. × 180.

FIG. 13.—Section of the eye showing reduplication of the elastic lamina in arteriole and old haemorrhagic exudate in subchoroid layer. × 800.

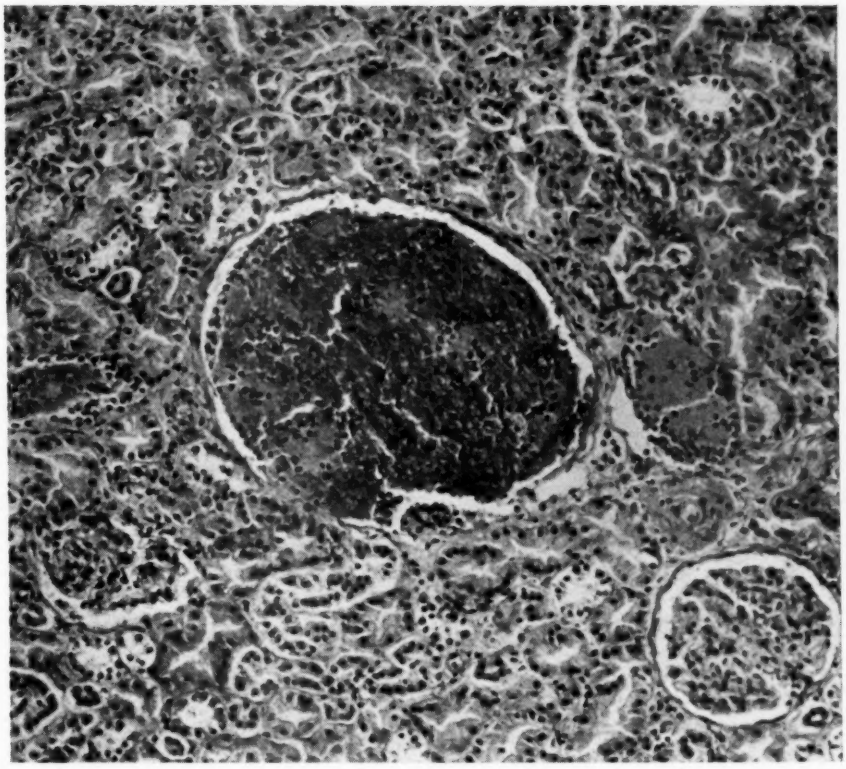

FIG. 12.

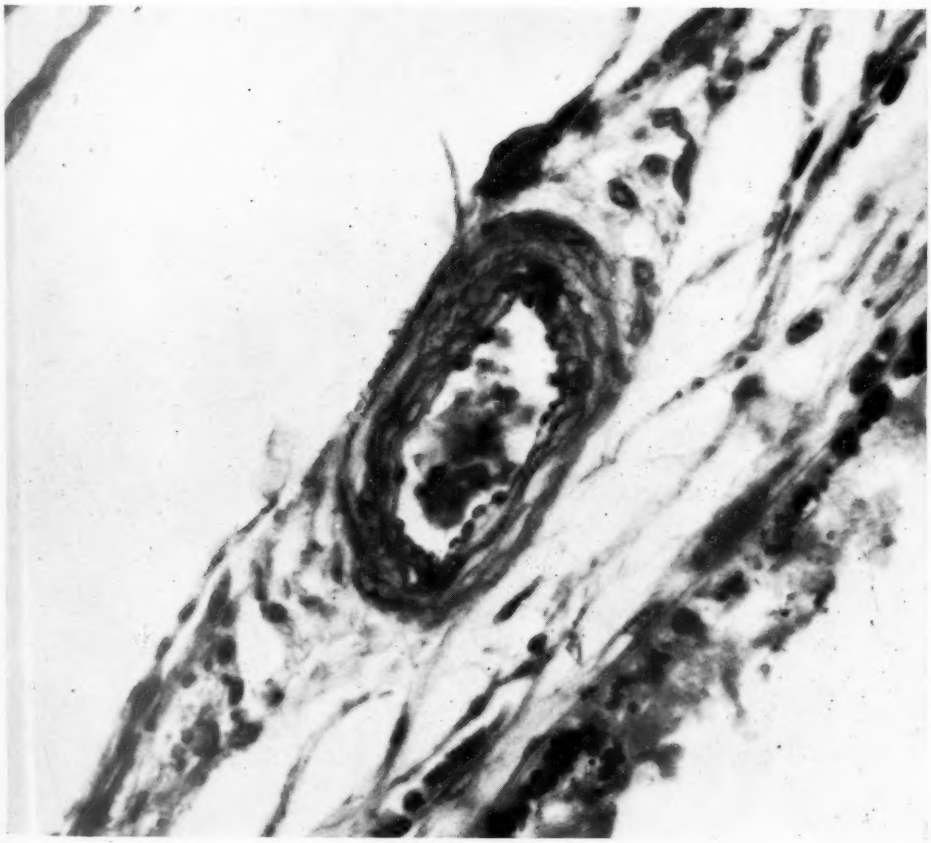

FIG. 13.

## Discussion

The characteristic paroxysmal attacks, with abdominal pain, vomiting, tachycardia, sweating, restlessness and collapse which the boy's doctor first described when his patient was 7 years of age disappeared when his blood-pressure became sustained. He was still liable to hyperadrenalinism on occasions which might have been expected to produce it: at times of emotional stress or by local stimulation to the tumour as in the injection of perirenal air. On examination by the visiting physician his face, hands and feet became a bright pink and the degree of sweating on his trunk was remarkable, the examining hands being literally wet. His irritability extended to the voluntary musculature, so that contraction of the abdominal wall always made examination difficult. It is now well recognized that the paroxysmal attacks may occur late in the disease (Cole, 1950), and that they may never occur at all; but that they may occur early, and then entirely disappear for three years while the patient remains comparatively well, as in M.B.'s case, is certainly unusual. It appears possible though not certain that the paroxysmal phase in this boy may have had some connexion with the massive retinal exudate which was the presenting sign in 1946. If this represented an extreme degree of hypertensive retinal change, it was certainly greater than is observed at any stage of essential hypertension in adults. It is remarkable that the retinal exudate regressed with the passing of the paroxysmal phase. Bruce (1947) paid especial attention to the retinal changes in the three children operated on by Cahill who showed exudate of much lesser extent than M.B., and he concluded that the fundal changes in these children were identical with those of essential hypertension in adults. Mr. Affleck Greeves, who saw him two years after the fundal changes had subsided, gave his opinion that the ophthalmoscopic appearances were those of a healed choroiditis. This was not, however, the opinion of several ophthalmologists who saw the boy in 1947.

The clinical diagnosis of phaeochromocytomata in children should present little difficulty if the sphygmomanometer is used routinely in their examination. The boy's appearance was so remarkably like that of a baby with pink disease as to suggest that hyperadrenalinism may play a part in the mechanism of acrodynia, in which restlessness, irritability, pink extremities, sweating, hypertension, and tachycardia are also cardinal signs.

The benzodioxane test has recently been exposed to some criticism because it has occasionally failed to yield a positive result when phaeochromocytomata are present (Roth and Kvale, 1949; Prunty and Swan, 1950); because it has occasionally yielded a positive result when other conditions are the cause of the hypertension (Taliaferro, Adams, and Haag, 1949); and because serious side-effects are sometimes produced (12% of the 75 cases of Wilkins, Greer, Cuthbertson, Halperin, Litter, Burnett, and Smithwick 1950). It provides, however, an indispensable confirmation of diagnosis, and it has a degree of specificity unusual in most clinical or laboratory diagnostic examinations. No death has been reported from its use, and it has now been very widely used. The localization of the tumour is difficult, and may be dangerous. The injection of perirenal air, first utilized by Cahill, is a method of great value but it may fail to locate tumours in the adrenals, and it has only once located an extra-adrenal tumour. It is not employed in the Mayo Clinic for localization of adrenal tumours on account of the dangers of the method; it is probable that the danger is inversely proportional to the experience of the operator, and Cahill has continued to regard it as safe and reliable. The alternative method is the diagnostic laparotomy, and since this caused the death of M.B., it would appear wiser that, in future, any tumours discovered should be removed at the first laparotomy.

Spear and Griswold (1948) showed that dibenamine hydrochloride (N,N-dibenzyl-beta-chlorethylamine hydrochloride) would depress the blood-pressure in phaeochromocytomata for 11 hours, after which the pressure rose to previous levels. Koffler *et al.* (1950) have recently confirmed the action of dibenamine in a boy. Grimson, Longino, Kernodle, and O'Rear (1949) report a successful operation in a boy aged 10 in whom they injected an adrenalytic substance (C7337) six times during the operation to prevent the fluctuations of blood-pressure which occur during the operation. Our experience with M.B. suggests that this is one of the ways in which surgery may be made increasingly safe for these patients. The post-operative collapse which follows the removal of these tumours is well recognized. Professor H. J. Burn (personal communication) states that this collapse is due to the depression of impulses through the sympathetic ganglia by the discharge of adrenaline throughout the operation, so that the normal stream of tonic impulses is unable to reach the blood vessels.

The action of such substances as benzodioxane was thought to be adrenalytic, but it is now believed that they compete with adrenaline and allied pressor agents by occupying the adrenaline-specific receptor. The action of benzodioxane is transient, but dibenamine is thought to combine irreversibly with the adrenaline-specific receptor. Both Goldenberg

(personal communication quoted by Prunty and Swan, 1950), and Howard and his colleagues have found that benzodioxane blocks the specific receptors for both adrenaline and nor-adrenaline. Prunty and Swan (1950) have recently reported their results in the use of benzodioxane in a series of normal subjects undergoing adrenaline and nor-adrenaline infusions. The fall in blood pressure was transient and inconsiderable, and both tachycardia and vasodilatation occurred. They suggested that the increased cardiac output in their cases may have more than balanced the pronounced vasodilatation. Such a mechanism may explain the occasional failure of the test with benzodioxane in the presence of phaeochromocytoma. It is apparent that the blocking action of adrenalytic substances, and the effects of adrenaline and nor-adrenaline on the circulation both require further elucidation.

Pamela Holton at Oxford (1949) was the first to identify nor-adrenaline in these chromaffin tumours, and she suggested that it might be the cause of the paroxysmal attacks since it has a greater pressor activity than adrenaline. Adrenaline causes vasodilatation with increased cardiac output and consequent hypertension; nor-adrenaline acts as a vasoconstrictor without effect on cardiac output. The hyperglycaemic effect of nor-adrenaline is less than that of adrenaline in the ratio of 1:8. It is thought that the content of nor-adrenaline in the secretion from the healthy adrenal medulla is less than 20%. Goldenberg and Faber (1949) have shown by chromatography that 50 to 90% of the adrenaline fractions of these chromaffin tumours was composed of nor-adrenaline. These observations have been confirmed by subsequent workers.

A notable advance in the diagnosis of phaeochromocytoma has recently been made by von Euler in Stockholm. By a biological estimation of the catechols in the urine, he and Engel (1950), have shown that the output of urinary adrenaline and urinary nor-adrenaline is greatly increased (normal 20 to 40 mg. a day) when a phaeochromocytoma is present.

The endocrine side effects of the tumours are interesting, but difficult to explain. The hyperglycaemia (as demonstrated in M.B.) has been suggested to be due to stimulation of pituitary hormones by adrenal cortical activity. It would seem easier to attribute it to continuous mobilization of liver glycogen by adrenaline. The evidence provided by the output of urinary 17-ketosteroids in M.B. suggests that there was adrenocortical depression. This was accompanied by a low output of gonadotrophins, and Dr. Hain suggested that both these results may be explained by hypopituitarism. Adrenaline (Corcoran and Page, 1948) stimulates the production of adrenocorticotrophic hormone by the anterior pituitary. Koffler *et al.* found a high output of gonadotrophins in the urine of their patient. The child aged 2 years described by Neff *et al.* had evidence of hypercorticism in the presence of a phaeochromocytoma. It is apparent that these assays, though interesting to record and to speculate upon, cannot yet be understood.

## Summary

A case is described of multiple phaeochromocytomata (four tumours) occurring in a boy aged 11. A characteristic paroxysmal phase lasted from the age of $6\frac{1}{2}$ to 8 years of age. For a further three years the boy was in good health, except for symptoms of sweating, restlessness, nocturnal enuresis, and occasional fatigue. This was the phase of sustained hypertension. The third phase of hypertensive heart failure would not have been long delayed if he had not died after a diagnostic laparotomy. The clinical signs and electrocardiographic changes of advanced hypertensive disease were confirmed by the state of the arteries and arterioles at necropsy.

References are given to other examples in the literature of phaeochromocytomata in children diagnosed during life.

Massive retinal exudate was coincident with the hypertensive phase. The amount of exudate was much greater than has been described either accompanying phaeochromocytoma or essential hypertension. The exudate regressed during the phase of sustained hypertension. The retinal changes were associated with a pleocytosis in the cerebrospinal fluid. Expert ophthalmological opinion is not agreed as to whether the changes in the fundi were related to paroxysmal hypertension.

The benzodioxane test gave a positive result in this boy, but the injection of perirenal air was not completely successful.

The diagnosis of these tumours is easier in children than it is in adults, if the repeated use of the sphygmomanometer is not forgotten.

The excretion of gonadotrophins and 17-ketosteroids was low in this boy, and the significance of this fact is discussed. The pharmacological nature of the tumours is described.

I am grateful to Dr. A. M. Hain for the endocrine assays, to Professor H. J. Burn for some advice in pharmacology, to Mr. A. J. Wilson for his surgical help, to Dr. I. Mackenzie for the necropsy reports, to Mr. T. E. A. Carr and Mr. Affleck Greeves for access to their ophthalmological records, to Dr. G. Q. Chance for radiological reports and to Dr. Watkins, my house-physician, for some bedside investigations.

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(Description of phaeochromocytoma in children diagnosed during life marked with a dagger.)

# FAMILIAL RENAL INSUFFICIENCY

BY

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(Received for Publication February 5, 1951)

The picture of chronic renal insufficiency in childhood is not common, and instances of more than one member of a family with this picture are comparatively rare. Mitchell (1930), in an exhaustive review of the literature of chronic interstitial nephritis in childhood, quotes 14 instances in which more than one child in the family was affected. Graham and Hutchinson (1941) have described a family in which three or probably four out of eight children suffered from this condition. Rinkoff, Stern, and Schumer (1939) reported the death from renal failure in early adult life of three brothers: necropsy on two of them confirmed the presence of chronic glomerulo-nephritis, but death apparently occurred in all three cases soon after the symptoms appeared, and there is no evidence indicating the time of onset. Hawkins (1950) has recently described the occurrence of chronic nephritis in association with a variety of congenital defects in two brothers and in one daughter of each of them. In this family the renal lesion appears to have been relatively benign, as two of the affected members were over 40 years of age, and all of them were alive.

In view of the comparative rarity of reports on familial nephro-sclerosis, it may be of interest to report the histories of a family of six children, of whom one was found at necropsy to have a hypoplastic horseshoe kidney, and two others subsequently died of chronic renal failure.

## Family History

Both parents, who are not related to one another, were healthy at the relevant period in the history, though the mother has now (1950) developed diabetes mellitus. Both were in their early twenties when their first child was born. The father was one of seven brothers of whom two died aged 9 years and 7 years, one of meningitis, and one of 'ulcers of the stomach.' (The father is unable to amplify this description.) The mother has six sisters and two brothers, all alive and healthy. Neither parent knows of the occurrence of kidney disease among members of previous generations of their families.

Eleanor S., the eldest child, was born in 1927. She was admitted to this hospital at the age of 5 years suffering from enuresis, but no evidence of organic disease was found. She was married at the age of 17, and was admitted to Aberdeen Maternity Hospital in the sixteenth week of pregnancy with albuminuria. This cleared up with rest, and she was discharged, but readmitted one month later with pyelitis. An intravenous pyelogram at this time showed normal concentration and renal outlines. The pyelitis settled rapidly under treatment with alkalis. She is now said to be healthy, but she refused to be examined. Her child was examined at the age of 17 months, and no abnormality was found. He is said to be excessively thirsty, and to pass much urine, but a specimen examined had a specific gravity of 1022, and was free from albumin and abnormal deposit.

**Case 1.** William S. was born in 1928. This boy died in this hospital on December 18, 1930, at the age of 2 years and 9 months of bronchopneumonia following tonsillectomy. His case notes and necropsy report are now missing, but from entries in the notes of the subsequent children it appears that at necropsy he was found to have a hypoplastic horseshoe kidney with pyelo-nephritis. Although pus had been found in the urine on one occasion, serious renal disease was not suspected before his death. Professor J. Craig, under whose care the child was, confirms these details from memory.

Alice S. (Case 2) was born in 1930.

James S. was born in 1933. He was admitted to this hospital at the age of 2 months with pyelitis, at 4 years with enuresis, and again at 11 years with pyelitis. His urinary output and specific gravity were normal during each admission, and the two infections cleared up rapidly. Physical examination at the age of 13 years was negative apart from the finding of a blood pressure of 132/96, and a suggestion of palpable sclerosis of the brachial arteries. The urine was normal, though of low specific gravity at the first examination. A subsequent morning specimen had a specific gravity of 1019, and contained scanty hyaline casts. The blood urea was 38 mg. %, and a skiagram of the abdomen showed renal shadows of normal size.

Gordon S. was born in 1935, and is the only member of the family who has no history of disease of the urinary tract. On examination at the age of 11 years, no abnormality was found, apart from a slightly raised blood pressure (135/90). A morning specimen of urine had a specific gravity of 1014, and contained scanty hyaline casts. His blood urea was 32 mg. %.

Kathleen S. (Case 3) was born in 1940.

Mrs. S. has had one subsequent pregnancy which was artificially terminated.

### Case Reports

**Case 2.** Alice S. was first admitted to this hospital on November 24, 1931, at the age of 18 months with a history of excessive thirst, polyuria, constipation, and occasional vomiting from the age of 9 months. Her previous history was not significant. On examination she weighed only 19¼ lb., but was in good general condition and there were no abnormal findings. Her blood pressure was 85/?.

The following investigations were made:

URINE. Specific gravity 1010; no albumin; deposit of pus cells and occasional red blood cells. On culture a scanty growth of haemolytic streptococci was seen. On daily examination during the next three weeks the specific gravity never rose above 1010, and scanty pus cells were seen occasionally. The 24-hour output varied between 19 and 42 oz.

Blood urea was 43 mg. %. A urea concentration test gave the following results:

| | | |
|---|---|---|
| Initial specimen | .. .. | urea 0·7% |
| After 5 g. urea after | 1 hour .. | „ 0·5% |
| „ „ | 2 hours .. | „ 1·5% |
| „ „ | 3 hours .. | „ 1·0% |

Cystoscopy and cystography showed no abnormality.

She was next admitted in April, 1934, complaining of occasional attacks of frontal headache and dizziness during the previous year. She was then a small child weighing only 30 lb. at the age of 4 years, but was still in fairly good general condition. Her blood pressure was 115/95. Her urine specific gravity varied between 1005 and 1012, and her output between 20 and 56 oz. in 24 hours. The urine was consistently free from albumin, and the only significant deposit seen was an occasional hyaline cast. The blood urea was 69 mg. %, and the Wassermann reaction was negative. Intravenous pyelography with 10 ml. 'uroselectan' showed no abnormality in shape or size of the right kidney, but marked delay in secretion, the maximum concentration being seen at 1 hour and 20 minutes. The left kidney was obscured by gas throughout the examination.

The child was subsequently readmitted in November, 1934, November, 1935, May, 1936, September, 1936, May, 1939, November, 1940, January, 1941, and September, 1941. The usual reason given for admission before 1940 was recurrent attacks of colicky abdominal pain sometimes accompanied by diarrhoea and vomiting; subsequent admissions followed periods of generalized convulsions. Polyuria and thirst were constant symptoms throughout. Radiological evidence of renal rickets was first seen in April, 1937, when she was 7 years old. The optic fundi remained normal until January, 1941, when it was noted that both optic discs were pale, that there was marked exposure of the choroidal vessels, and that the arteries appeared narrow: there were no haemorrhages nor exudates. The details of her progress during these admissions can most easily be followed in tabular form (Table 1).

Her final admission was on January 13, 1942, following a series of convulsions during the preceding two days. On examination she appeared pale and drowsy and showed marked air hunger. She vomited persistently, passed no urine, and died within 12 hours of admission.

NECROPSY. Necropsy was performed 12 hours after death. Both kidneys were greatly reduced in size, the right weighing 15 g. and the left 40 g. (average weight of normal kidney at age 11 years, 95 g.). The capsules could be stripped, and the subcapsular surfaces were pale and coarsely granular. The kidneys were studded with small, pearly white nodules, each about 0·5 cm. in diameter. There was no gross dilatation of the renal pelves or ureters. There was marked cloudy swelling of the liver. The heart showed slight left ventricular hypertrophy. The epiphyseal lines in the femur were wide and slightly irregular. No other abnormalities were noted.

The histology is discussed under case 3.

**Case 3.** Kathleen S. was first admitted to this hospital on February 11, 1942, at the age of 16 months with a history of excessive thirst, polyuria, constipation, and failure to thrive for several months. She had been born three weeks prematurely, and her birth weight was 4 lb. Her development at first appeared normal. Since weaning, she had been unwilling to eat solid foods, but had always appeared thirsty. On examination she was seen to be an irritable child with a rather waxy skin, but no other abnormality was found. Her height was 26 in., and her weight 21 lb. Twelve successive 24-hour specimens of urine were examined: the specific gravity ranged from 1006 to 1012; traces of albumin were present in two specimens, and no casts or cellular deposits were seen.

Her further progress during the next four years can again most easily be summarized (Table 2).

Her tonsils and adenoids were removed in February, 1945, on account of recurrent attacks of tonsillitis. Radiological evidence of rickets was first detected in February, 1946, and by June of that year knock-knee was apparent. About this time she began to complain of pain in her legs and became unwilling to walk.

By July, 1946, she was having frequent attacks of vomiting, and on July 31, she was finally admitted with a history of constant nausea and drowsiness, and occasional convulsions during the preceding two weeks. On admission she appeared pale and drowsy; no oedema was present; the optic fundi were normal; her blood pressure was 120/80. Urine specimens were difficult to collect owing to continual incontinence, but on one occasion the specific gravity was 1010; no albumin was present but there were considerable numbers of pus cells.

| | | |
|---|---|---|
| Blood chemistry | Blood urea .. | 392 mg. % |
| | Plasma cholesterol | 184 mg. % |
| | Serum calcium .. | 6·4 mg. % |
| | Serum phosphorus | 8·0 mg. % |
| | Serum phosphatase | 33 units |

TABLE 1

SUMMARY OF CASE 2 DURING ADMISSIONS BETWEEN 1934 AND 1941

| Date | Age | Height (in.) | Weight (lb.) | Blood Pressure | 24-hr. Urine Output (oz.) | Urine Specific Gravity* | Blood Urea (mg. %) | Other Points |
|---|---|---|---|---|---|---|---|---|
| Nov., 1934 | 4½ | | 29 | 82/45 | 50–65 | 1002–1010 | 71 | Urine : albumin negative<br>Slight oedema, ankles. |
| Nov., 1935 | 5½ | | 31½ | 108/62 | 50–90 | 1002–1010 | 120 | Urine: occasional trace albumin; day and night volumes approximately equal.<br>Blood Ca 10·2 mg. %<br>Phosph. 5·9 mg. % |
| May, 1936 | 6 | | 33¼ | 132/96 | 44–70 | 1005–1010 | | Urine: albumin negative. |
| Sept., 1936 | 6¼ | | 30 | 118/76 | 35–67 | 1002–1008 | | Urine: trace of albumin. |
| May, 1939 | 9 | | | | | 1002 | 125 | Urea clearance 9%<br>Blood Ca 8·6 mg.%<br>Phosph. 6·2 mg.%<br>Phosphatase 30 units |
| Nov., 1940 | 10½ | 45¼ | | 120/82 | | 1004 | 220 | |
| Jan., 1941 | 10¾ | 46½ | 46 | 145/90 | 40–92 | 1003 | 136 | Urine: trace of albumin.<br>Blood Ca 8·1 mg.%<br>Phosph. 4·0 mg.% |
| Sept., 1941 | 11¼ | 46½ | 50 | 140/90 | 30–50 | 1003 | 192 | Urine: trace of albumin.<br>Blood Ca 7·0 mg.%<br>Phosph. 6·8 mg.%<br>Cholesterol 180 mg.% |

* The very low figures quoted were confirmed on several occasions during the later admissions by the Natural Philosophy Department, Aberdeen University.

TABLE 2

SUMMARY OF CASE 3 DURING ADMISSIONS BETWEEN 1943 AND 1946

| Date | Age | Height (in.) | Weight (lb.) | Blood Pressure | 24-hr. Urine Output (oz.) | Urine Specific Gravity | Blood Urea (mg.%) | Other Points |
|---|---|---|---|---|---|---|---|---|
| Sept., 1943 | 3 | 34½ | 28¼ | | | 1004–1018 | 45 | |
| Sept., 1944 | 4 | | 28 | 140/110 | 23–43 | 1002–1008 | 102 | Urine: albumin negative. |
| Feb., 1945 | 4¼ | | | 128/92 | 18–26 | 1011 | 75 | Urine: albumin negative. |
| Feb., 1946 | 5¼ | | | | | 1003 | | Urine: trace of albumin. |
| June, 1946 | 5¾ | | | 135/100 | | 1005 | 358 | Urine: albumin negative and pus cells. |

Following intermittent convulsions, the child died on August 4, 1946.

NECROPSY. Necropsy was performed 24 hours after death. The kidneys were the only organs showing significant abnormality. The combined weight of the two kidneys was 70 g. (normal at this age 130 g.). The capsules stripped readily leaving a smooth but pale surface; the cut surface showed a loss of definition between the cortex and the medulla, and some small, scattered cysts. The blood vessels appeared normal.

HISTOLOGY. Both cases alike presented the histological characteristics of chronic pyelo-nephritis (Fig. 1 and 2). Both showed hyalinization of many glomeruli accompanied by atrophy of the related tubules. In case 2 the proportion of hyalinized glomeruli was greater, and all the surviving glomeruli were considerably hypertrophied, while their capsules were distended as in a hydronephrosis (Fig. 3); arteriosclerosis and arteriolosclerosis were prominent features (Fig. 4); no tubular cysts were present. In case 3 numerous small cysts lined by moderately hyperplastic cubical epithelium were noted (Fig. 5); the majority of the surviving glomeruli were normal in size, and only a small number of them showed a conspicuous degree of hypertrophy (Fig. 6); neither arteriosclerosis nor arteriolosclerosis was a prominent feature. It is emphasized that, in both cases alike, all the surviving glomeruli, whether hypertrophied or not, showed no stigmata of an antecedent glomerulo-nephritis.

## Discussion

The clinical picture of renal sclerosis in childhood is an uncommon one. It may result from chronic glomerulo-nephritis or from chronic pyelo-nephritis; it may be associated with congenital cystic disease; it is probably very rarely secondary to essential hypertension; in a considerable proportion of cases it appears insidiously, often at a very early age, without any history suggestive of previous renal disease.

In the two children of this family about whom detailed information is available, there was no definite evidence of the nature of the original disease process. In both, the history of thirst and polyuria indicated the onset of renal failure before the end of the first year of life. In neither was there any history suggestive of an acute attack of glomerulo-nephritis, nor does the histological picture support this diagnosis. Moreover, when glomerulo-nephritis does occur at this age, it tends, in my experience, to be severe and unlikely to pass unnoticed. The histological appearances would support a diagnosis of pyelo-nephritis, and indeed establish its presence in both cases at the time of death, but the clinical evidence suggested that this was not the primary condition. In the course of a very large number of urine examinations in both cases, pus cells in significant numbers were reported on isolated occasions only. In neither case was there any evidence at necropsy of congenital or other conditions predisposing to urinary stasis which is associated with chronic urinary infection in such a large proportion of cases in childhood. Furthermore, pyelo-nephritis is usually known to have been present for a number of years in those cases in which it ultimately leads to renal sclerosis. While it seems improbable that it could produce symptoms of renal failure before the end of the first year of life, this possibility cannot be absolutely excluded; but, even if it be admitted that the essential pathological process is a pyelo-nephritis, the fact that this condition has occurred in three members of one family in the absence of gross urinary stasis surely suggests that the kidneys in the first place must have been in some way abnormal. The clinical evidence seemed to indicate that the pyelo-nephritis was a secondary condition.

Arteriosclerosis and arteriolosclerosis were prominent on histological examination only in case 2 (Fig. 4), but in neither case was anything more than a very moderate degree of hypertension observed even in the terminal stages, while in case 2 the blood pressure was certainly normal after the picture of renal failure was established. This is in keeping with the usual finding in cases presenting the picture of this type of renal failure in the first few years of life (Spence and Davison, 1949). Ellis (1942), in his survey of the natural history of Bright's disease, has suggested that 'chronic interstitial nephritis, as we have known it in the past, is merely the result of hypertension.' This may well be true of those cases seen in adult life or later childhood in which the blood pressure is usually found to be significantly raised whatever the nature of the primary disease. In infancy and early childhood, however, it seems that some other factor must be capable of producing the clinical and histological picture of chronic interstitial nephritis.

In cases of renal sclerosis which arise insidiously without any previous history of renal disease, it is sometimes assumed that there has in fact been a preceding attack of glomerulo-nephritis with symptoms mild enough to escape detection. There seems no justification for this assumption in cases such as are the ones under discussion, for in clinically obvious cases of acute nephritis in childhood, where complete resolution does not occur, progress towards the final picture of renal sclerosis is slow, and this stage is rarely reached before the age of puberty. There seems no good reason to suppose that an attack of acute nephritis mild enough to remain undetected will result in the more rapid onset of sclerosis and, even if the possibility of an attack of acute nephritis *in utero* be admitted, it seems highly improbable that it will result in the

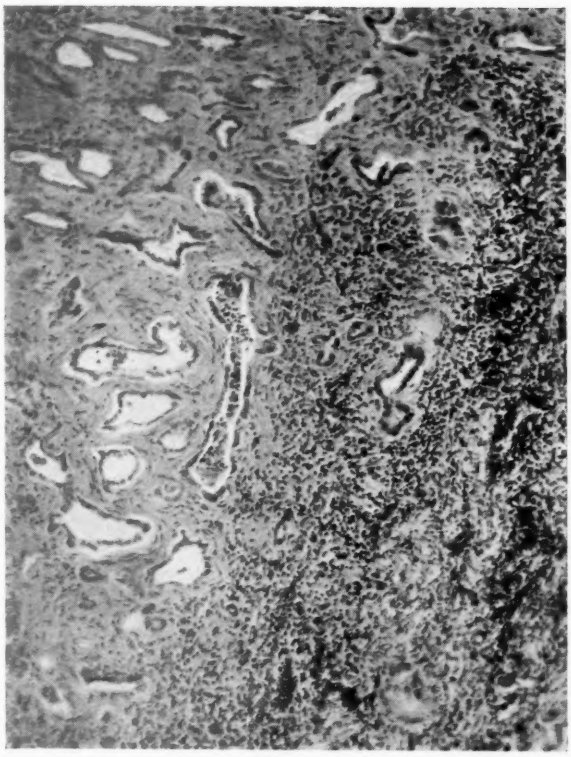

FIG. 1.

FIG. 2.

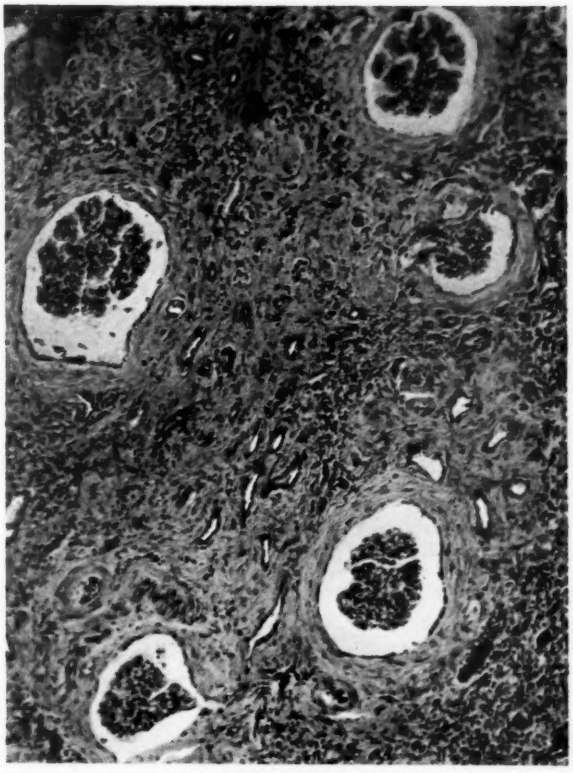

FIG. 3.

FIG. 1 (Case 2).—Pus in lumen of tubule; hyperaemia and round cell infiltration of interlobular septum (×90).

FIG. 2 (Case 3).—Chronic pyelitis. Pus in lumen of pelvis (×90).

FIG. 3 (Case 2).—Group of five glomeruli showing some dilatation of capsules and capsular fibrosis; notable absence of adhesions between tuft and capsule; interstitial fibrosis and atrophy of tubules (×90).

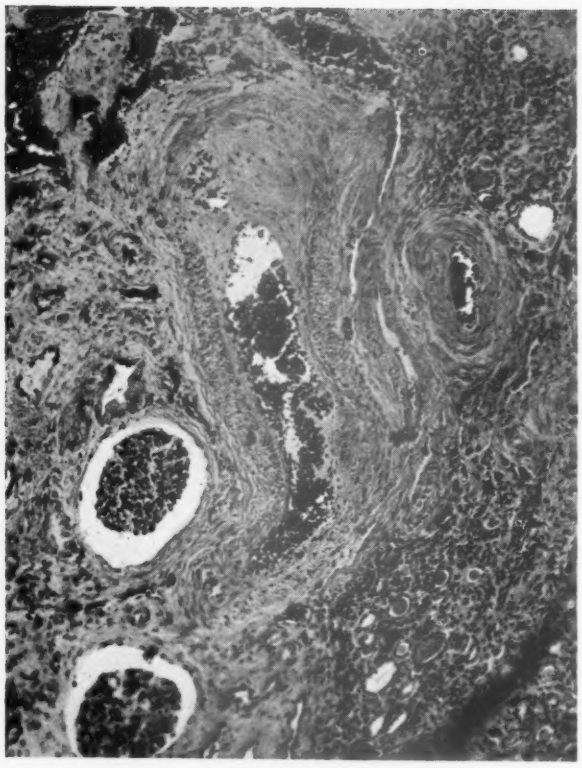

FIG. 4.

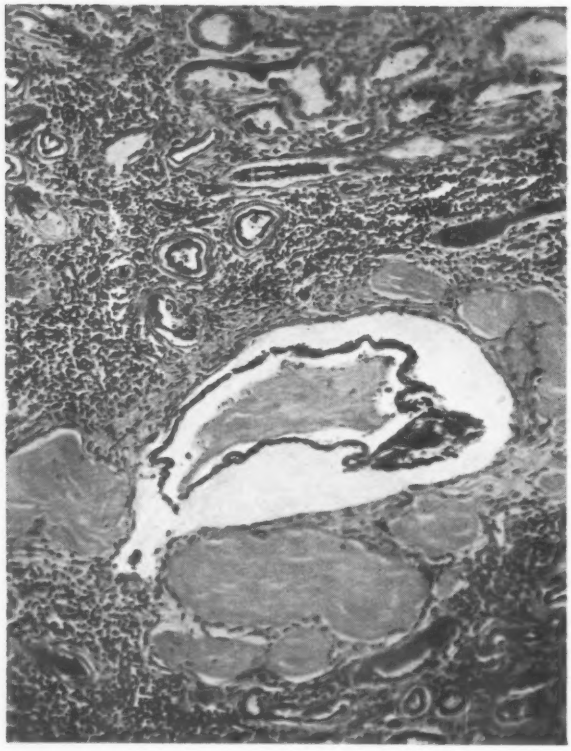

FIG. 5.

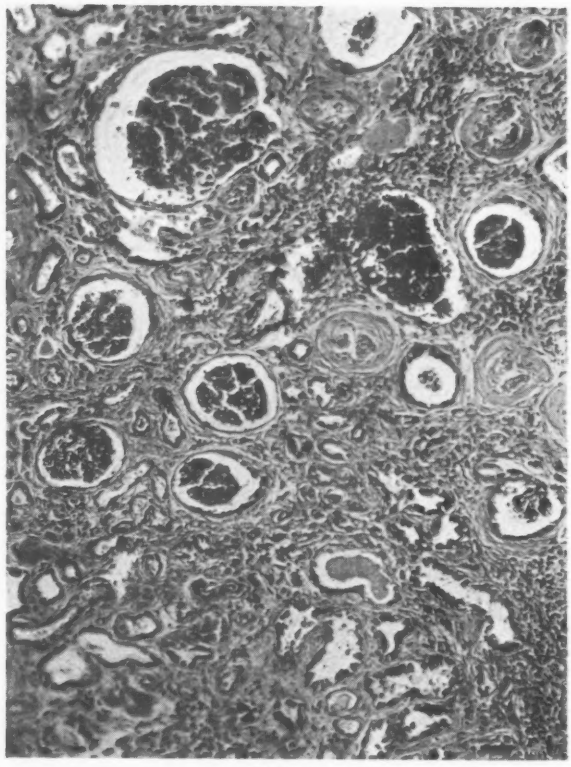

FIG. 6.

FIG. 4 (Case 2).—Sclerosed artery and two nearly normal glomeruli (×90).

FIG. 5 (Case 3).—Small cyst lined by hyperplastic cuboidal epithelium (×90).

FIG. 6 (Case 3).—Group of glomeruli, one of which is notably hypertrophied; other glomeruli sclerosed; related tubules atrophied (×90).

clinical picture of renal sclerosis before the age of one year.

Where, as in this instance, the syndrome appears in two members of one family in the first year of life, and in addition another member is known to have had congenitally abnormal kidneys, it suggests either the presence of some maternal factor capable of damaging the foetal kidneys *in utero*, or of a genetic factor resulting in the development of inferior or abnormal renal tissue. The first possibility would seem unlikely, as there was an interval of 12 years between the birth of the first and the last of the affected children, and as, during this period, the mother herself remained in good health, and gave birth to two children with apparently normal kidneys. While it seems likely, therefore, that the defect was genetically determined, its nature remains obscure and histological examination threw no light on this aspect of the problem. It is indeed unlikely that the problem will ever be solved on the basis of necropsy findings in children dying of chronic renal failure, for the picture then is of general atrophy of renal tissue accompanied by interstitial fibrosis. Evidence as to the nature of the defect might be obtained by examination of kidney tissue from stillbirths or abortions occurring in a family where a case of renal sclerosis in early life is already known. From the family here reported, no further information can be obtained, as the mother has already been sterilized.

The occasional occurrence of several cases of renal sclerosis in one family supports the view that genetic factors may be responsible for some, at any rate, of the single cases of this syndrome declaring itself in the early years of childhood. For the present the title ' congenital hypoplastic kidneys ' suggested by Spence and Davison (1949) is probably the most appropriate to describe this condition, although it is by no means certain that this is a true primary hypoplasia rather than an inflammatory or degenerative process.

**Summary**

The history is given of a family in which two members developed chronic renal failure in infancy, and a third died at an early age and was found to have a hypoplastic horseshoe kidney.

It is suggested that in these cases renal sclerosis is the result of some congenital defect or weakness of the kidney tissue.

I wish to express my thanks to Professor John Craig for advice and encouragement in the preparation of this report, and to Professor John S. Young for the necropsy and histological reports and for the accompanying microphotographs.

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## ADDENDUM

Since this paper was submitted another family with a somewhat similar history has come to my notice. The parents are both alive and healthy; they have had 11 children, three boys and eight girls. Of these, numbers 4, 6, and 7 in birth order, all girls, died at the age of 7 or 8 years with symptoms of chronic uraemia. Necropsy confirmed the presence of renal sclerosis in all three. Number 9 in birth order, also a girl, has now appeared at the age of 8 years with a history of excessive thirst from the age of 18 months or earlier. She is in fair general condition; the blood pressure is 110/70, the blood urea 132 mg. %, and the serum phosphorus level 9 mg. %. The urinary output is high and the specific gravity of the urine rarely rises above 1006. Traces of albumin are occasionally present and there is no significant deposit. A urea clearance test showed 25% of normal clearance. It has not been possible to examine the remaining members of the family but specimens of urine from three of them, including the two youngest, were of fairly high specific gravity and contained neither albumin nor abnormal deposit.

# UNILATERAL RENAL VEIN THROMBOSIS TREATED BY NEPHRECTOMY AND POST-OPERATIVE HEPARIN

BY

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In the majority of cases renal vein thrombosis is secondary to dehydration, sepsis, or both, and has occurred in enterocolitis, diphtheria, umbilical sepsis, measles, and skin infections. It has been recorded as a sequel to pyelo-nephritis due to a spread from the glomerular to the renal vein. The renal vein may become secondarily involved as a result of thrombophlebitis in the vena cava, the spermatic, or the ovarian veins. This type, however, seems to be confined to adults, and is very rare in infancy.

Both sexes are equally involved. The age incidence is interesting in that 40% of cases occur in the first two months of life (Abeshouse, 1945).

In the neonatal period the commonest type of lesion is one in which the thrombotic process originates within the renal venous system subsequent to infection with dehydration.

The case described here is one of unilateral renal vein thrombosis diagnosed after observation and treated by nephrectomy.

### Case Report

On March 3, 1950, a boy weighing 10 lb. 6 oz. was born at full term; the delivery and pregnancy were normal. The Wassermann reaction was negative, Rh positive.

At birth the baby was cyanosed and did not cry well. He had multiple petechiae of the head, neck, and trunk. There was poor air entry into the lungs. A diagnosis of anoxia due to extensive atelectasis was made and continuous oxygen therapy was administered for three days. Afterwards his condition improved and he was breast fed normally.

On March 29, 1950, the mother insisted on discharging herself and the baby from the hospital. The weight of the baby was now 9 lb., and there was some redness and a slight discharge from the cord stump.

On April 4, 1950, the child was readmitted with a history of streaks of blood in the urine and vomiting for three or four days.

When the baby was examined he weighed 8 lb. 6 oz., and his temperature was 101·2° F. There was blood-stained mucus on the napkin; this was not mixed with the canary yellow stool, which was normal in appearance. The child's general condition showed him to be pale and quiet with evidence of dehydration. His chest and heart were normal; his abdomen was normal in appearance and movements. The umbilicus was clean and dry. Palpation revealed a large firm mass extending from the level of the costal margin to the iliac crest on the left side. The mass was perfectly smooth in outline and no notch could be felt. It conformed in outline to a renal swelling and could be displaced from the loin. The mass was obviously painful, and any palpation caused marked distress. No other abnormality could be found on examination. The right kidney was not palpable.

On rectal examination the mass could be felt in front of the rectum at the pelvic brim. No blood was seen on the examining finger. During the examination the child passed a quantity of urine which was preceded by the passage of a blood-stained mucous clot.

Further investigations gave the following results:

A radiograph of the abdomen was negative. A blood count gave R.B.Cs., 4·5 m.; Hb., 95%, W.B.Cs., 19,400 (neutrophils 63%, lymphocytes 30%). Microscopic examination of the urine showed one or two red blood cells, a large excess of leucocytes, coliform organisms, but no casts. On culture only *Bact. coli* were found.

In view of a large firm tumour of sudden origin in an infant, the differential diagnosis of Wilms' embryoma, infected haematoma of the kidney, or renal vein thrombosis was made. The history of cord infection and vomiting, together with clinical evidence of dehydration, blood-stained and heavily infected urine, and raised temperature, was more in favour of a renal vein thrombosis. The leucocytosis of 19,000 could be within normal limits.

Further blood examinations were made with a view to confirming a diagnosis of thrombosis, and these showed bleeding time, 7 min.; clotting time, 2½ min.; prothrombin time, 15 sec.; prothrombin control, 15 sec.; prothrombin index, 100%.

Although these findings were normal it was thought that the history and clinical findings were sufficient to diagnose a unilateral renal vein thrombosis.

The baby was prepared for exploratory operation.

**Pre-operative Treatment.** Hartmann's solution, 600 ml., was given subcutaneously; 500,000 units of penicillin were given at once and a further 100,000 units six-hourly. After the infusion the general condition

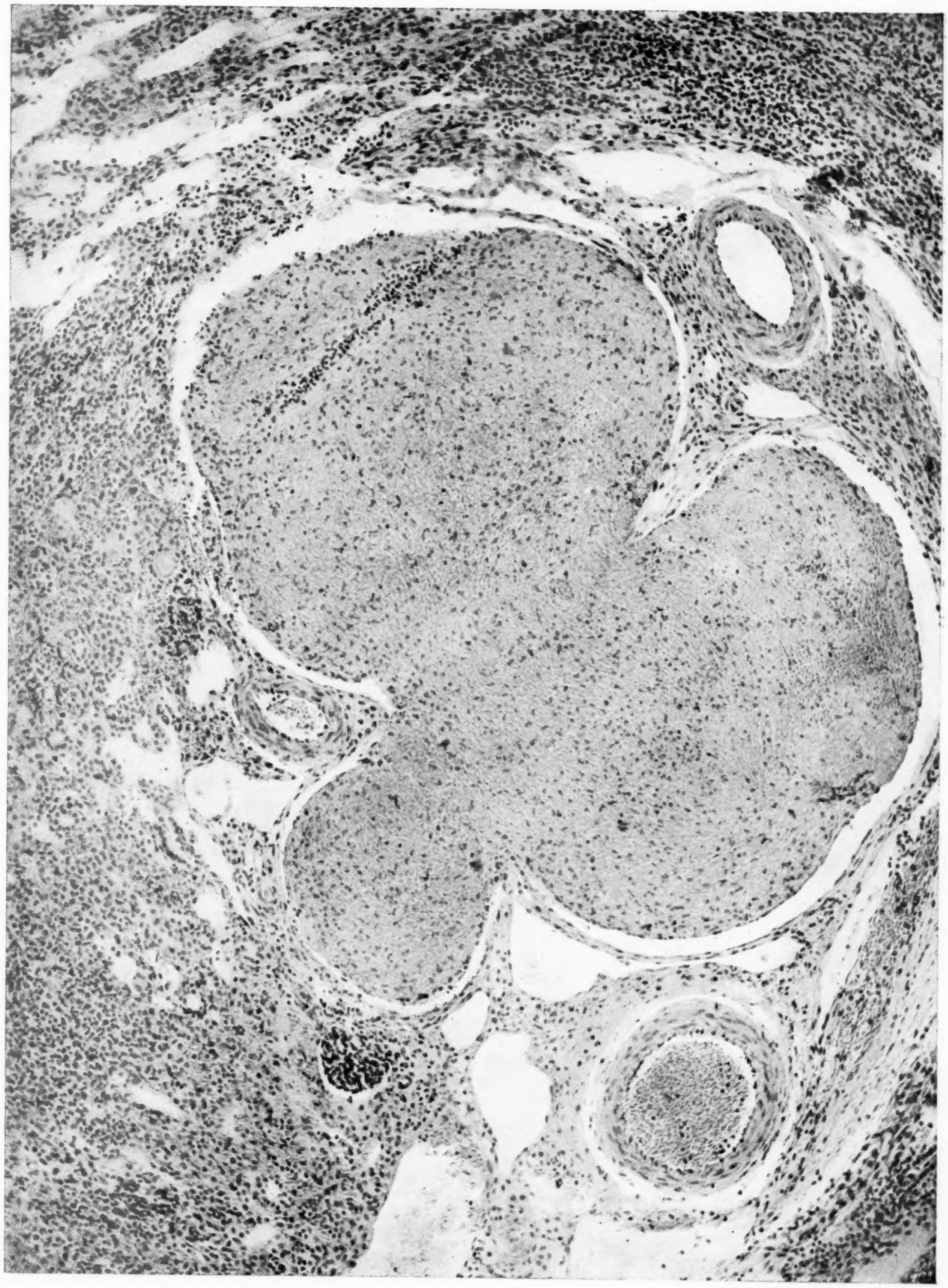

FIG. 1.
Section showing infected thrombus filling lumen of a vein.

improved considerably and urine was excreted in good quantity.

**Operation.** The operation was performed on April 5, 1950. Ether vapour and oxygen conducted by catheter under an open mask were used. The baby was placed in a semi-recumbent position with sandbags under the shoulder and pelvis. A left oblique renal incision was used with a right-angled extension upwards from the middle to allow free access to the renal pedicle.

The fascia of Zuckerkandl and fat were thickened and oedematous. Heavily bloodstained fluid was found between the fascia and the kidney, which was enlarged (more than twice the normal size) and haemorrhagic. Examination of the renal pedicle revealed a firm thrombus filling the whole of the renal vein. No thrombus was palpated in the vena cava.

The left kidney was packed off and the peritoneum opened at the anterior end of the wound. A transperitoneal examination of the right kidney showed this to be completely normal in size, shape, and consistency. The peritoneum was closed. The right kidney was normal and the renal output adequate, but the left renal vein was completely thrombosed and the urine heavily infected with *Bact. coli*, and nephrectomy was decided upon. The pedicle was dissected, and the renal vein ligatured about ¾ in. from the vena cava. The renal artery was normal and was ligated separately. The kidney was dissected free and removed. Then the wound was closed in layers with interrupted catgut sutures and the remaining cavity drained.

Chloral, 1 gr., was given six-hourly for three doses, and oxygen continuously. The right saphenous vein was cut down upon and 250 ml. blood given in five hours; saline, 150 ml., with hyalase was injected subcutaneously to follow the blood.

On April 6, 1950, the general condition was satisfactory. The infant was well hydrated, and passing urine normally. There was some distension of the abdomen. Small amounts of ½ normal saline and 5% 'casydrol' were given by mouth. Vitamin C, 500 mg., was given intramuscularly. A course of heparin, 5,000 units twice daily, was begun.

On April 7, 1950, the general condition was good. The baby passed a fatty stool. The abdomen was soft, and not distended. The next day, April 8, the drainage tube was removed satisfactorily. On April 9 there was a small haemorrhage from the wound. The patient's condition was satisfactory. The heparin was stopped. The baby's condition improved, and he was taking cow's milk from April 6, without any vomiting. He subsequently developed infection of the wound, which was proved on culture to be due to *Bact. coli* as in the original urinary infection. The wound infection delayed healing, but the general condition of the baby slowly improved.

By May 15, 1950, the wound was completely healed, but there was weakness in the underlying muscles due to the infection which caused a separation of the sutured muscles.

The baby was discharged from hospital on May 17, 1950, when his condition was quite satisfactory. He had steadily gained weight until on discharge he weighed 9 lb. 10 oz.

He was seen in the out-patient clinic on May 31, 1950, when progress had been steady, and his weight was 11 lb. 6 oz.

**Pathological Report.** The macroscopic appearance of the left kidney showed enlargement with well marked foetal lobulation. Beneath the capsule there were confluent areas of deep congestion, alternating with pale grey areas. The cortex and medulla appeared to merge in a uniform dark haemorrhagic mass, although at some points the differentiation could be clearly seen. The calyces were dilated and contained a mass of soft grey tissue which arbourized at the upper and lower pole. The renal vein contained a thrombus.

The microscopic appearance showed absolute infarction of the kidney substance by a septic thrombus travelling through branches of the renal vein (Fig. 1). There was widespread inflammatory change throughout the infarcted area.

## Discussion

Renal vein thrombosis is a rare condition and unilateral cases are still more rare. The condition should always be borne in mind when bloodstained urine is passed in the neonatal period. The presence of a renal swelling in neonatal life, particularly with infected urine, must also bring renal vein thrombosis into the differential diagnosis.

Predisposing factors of vomiting and infection are of extreme importance in making the diagnosis, though it is said that the condition can occur when these are absent. The predisposing factor is then said to be a condition of asphyxia with resulting general venous congestion and stagnation (Fallon, 1949).

Since most cases of renal vein thrombosis are diagnosed in the necropsy room, there is no uniformity of opinion regarding treatment.

Bilateral renal vein thrombosis usually terminates fatally, and surgery has no place in its treatment. Anti-coagulant therapy with heparin and dicoumarol has not yet been reported.

The role of surgery in the treatment of unilateral cases is of importance. Campbell and Matthews (1942) describe two cases of unilateral thrombosis treated surgically. They also advocate administration of vitamin K because of a low prothrombin level and haematuria. Administration of vitamin K, however, is absolutely contrary to the present conception of thrombosis and its treatment in general. In the case presented a low prothrombin level was not found: indeed, this was normal compared with a control. The risk of spreading thrombosis by administering vitamin K must be considerable and contra-indicates its use.

Nephrectomy in the unilateral case is not devoid of the risk that unsuspected thrombosis may have

started on the other side. Nephrectomy, however, can be life-saving where the thrombosis, as in most cases, is infective in origin and manifested by heavily infected urine. Fallon (1949) suggests this as the indication for nephrectomy.

The post-operative administration of heparin following nephrectomy may be of value in preventing thrombosis from occurring in the remaining kidney, or in arresting early thrombosis which may be present at the time of operation and impossible to detect by examination of the kidney at operation.

**Summary**

A classical case of unilateral renal vein thrombosis with treatment by nephrectomy and post-operative heparin is described.

The aetiology is briefly chronicled.

The treatment, particularly the role of surgery, is discussed.

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# BRITISH PAEDIATRIC ASSOCIATION

## REPORT ON THE TRAINING OF PAEDIATRIC CONSULTANTS, FEBRUARY 1951

(1) It is generally felt that, although the principles contained in the Interim Report of the Paediatric Committee of the Royal College of Physicians (1945) regarding the training of paediatric consultants are still accepted, certain alterations must now be made in detail because of the proposed ' compulsory year ' of residence, the continuation of National Service, and the general plan for registrarships which allowed for six years in various grades.

(2) It is emphasized that a paediatric resident post is not suitable during the compulsory year and that children's hospitals and children's departments should not be expected to supply resident posts of this type. Experience in general medicine as well as in surgery and obstetrics should be gained at this stage and it is recommended that, in all, the paediatric consultant should spend at least two years in general medical posts. National Service experience should only be recognized towards such two years if it has included essentially hospital work and only then for the period of such work.

(3) A paediatric resident post in the medical wards of a children's hospital or children's department of a general hospital of at least six months at senior house officer grade should follow at this stage and must be compulsory. Four years now remain for training, possibly five; this period should be spent mainly at an approved children's hospital or children's department of a general hospital and be devoted to appointments of registrar and senior registrar status. An appointment at some stage giving experience of the normal newborn baby should be obligatory, and this might take the form of a paediatric appointment in a maternity unit. Some practical experience of the infant welfare and school health services is most desirable, but it is not considered practicable to make appointments in these branches obligatory. One year of the total period might be devoted to travel or research or appointments giving experience in obstetrics, child guidance, infectious diseases, or laboratory work. A part of this period might be used in family practice and this should count towards the total period of paediatric training.

(4) It is agreed that some form of pathological work during the training is desirable, but it is not necessary to make a post in clinical pathology obligatory.